AZIENDA OSPEDALIERO UNIVERSITARIA MEYER

Delibera del Direttore Generale n. 266 del 26-05-2022

Proposta n. 512 del 2022

Oggetto: ERA-NET COFUND IN PERSONALISED MEDICINE – ERA PERMED (G.A. N. 779282) JOINT TRANSNATIONAL CALL 2021 PROGETTO “IMPLEMENTATION OF PERSONALISED MANAGEMENT IN NEPHROTIC SYNDROME” PER-NEPH – PRESA D’ATTO DEL PROGETTO E AUTORIZZAZIONE ALLA STIPULA DELLA CONVENZIONE CON REGIONE TOSCANA E UNIVERSITÀ DEGLI STUDI DI FIRENZE PER LA SUA REALIZZAZIONE (CUP G15F21001060002)

ERA-NET COFUND IN PERSONALISED MEDICINE – ERA PERMED (G.A. N. 779282) JOINT TRANSNATIONAL CALL 2021 PROGETTO “IMPLEMENTATION OF PERSONALISED MANAGEMENT IN NEPHROTIC SYNDROME” PER-NEPH – PRESA D’ATTO DEL PROGETTO E AUTORIZZAZIONE ALLA STIPULA DELLA CONVENZIONE CON REGIONE TOSCANA E UNIVERSITÀ DEGLI STUDI DI FIRENZE PER LA SUA REALIZZAZIONE (CUP G15F21001060002)

Dirigente: BINI CARLA

Struttura Dirigente: AMM. LEGALE E RAPPORTI CON UNIVERSITA

AZIENDA OSPEDALIERO UNIVERSITARIA MEYER
(Art. 33 L.R.T. 24 febbraio 2005 n. 40)
Viale Pieraccini, 24 - 50139 FIRENZE
C.F. P.Iva 02175680483

DELIBERAZIONE DEL DIRETTORE GENERALE

Oggetto	Progetto
Contenuto	Era-Net Cofund in Personalised Medicine – Era Permed (G.A. N. 779282) Joint Transnational Call 2021 Progetto "Implementation of personalised management in nephrotic syndrome" PER-NEPH – Presa d'atto del progetto e autorizzazione alla stipula della convenzione con Regione Toscana e Università degli Studi di Firenze per la sua realizzazione (CUP G15F21001060002)

Area Tecnico Amm.va	AREA TECNICO AMMINISTRATIVA
Coord. Area Tecnico Amm.va	BINI CARLA
Struttura	AMMINISTRAZIONE LEGALE E RAPPORTI CON L'UNIVERSITA'
Direttore della Struttura	BINI CARLA
Responsabile del procedimento	BINI CARLA
Immediatamente Esecutiva	SI'

Conti Economici			
Spesa prevista	**Conto Economico**	**Codice Conto**	**Anno Bilancio**
€ 65.000,00	**Costi per contributi Università attività di ricerca**	**4202280090**	**2022**

Estremi relativi ai principali documenti contenuti nel fascicolo		
Allegato	**N° di pag.**	**Oggetto**
1	66	Convenzione per la realizzazione del progetto "Implementation of personalised management in nephrotic syndrome" PER-NEPH

"documento firmato digitalmente"

IL DIRETTORE GENERALE
Dr. Alberto Zanobini
(D.P.G.R.T. n. 99 del 30 luglio 2020)

Visto il D. Lgs.vo 30/12/1992 n. 502 e sue successive modifiche ed integrazioni e la L. R. Toscana n. 40 del 24/02/2005 e s.m.i. di disciplina del Servizio Sanitario Regionale;

Dato atto:

- che con deliberazione del Direttore Generale n. 54 del 01.02.2021 è stato approvato il nuovo Atto Aziendale dell'A.O.U. Meyer, ai sensi dell'art. 6 del Protocollo d'intesa del 22.04.2002 fra Regione Toscana e Università degli Studi di Firenze, Siena e Pisa, con decorrenza dal 1.2.2021;
- che con deliberazione del Direttore Generale n. 55 del 1.02.2021 sono stati assunti i primi provvedimenti attuativi in relazione alla conferma/riassetto delle strutture complesse e semplici dotate di autonomia ed al conferimento dei relativi incarichi di direzione;
- che con deliberazione del Direttore Generale n. 56 del 1.02.2021 sono state assunte determinazioni attuative del nuovo Atto aziendale in relazione alla conferma/riassetto delle strutture Dipartimentali e/o a valenza dipartimentale, delle Aree Funzionali Omogenee, dell'Area Servizi dell'Ospedale, dell'Area dei Diritti del Bambino, dell'Area Tecnico Amministrativa ed al conferimento di relativi incarichi di direzione;
- che con successiva deliberazione del Direttore Generale n. 92 del 15.02.2021 si è provveduto ad assumere ulteriori disposizioni attuative relative all'organizzazione dell'AOU Meyer in ordine alle Strutture semplici Intrasoc, Unità Professionali, Uffici e Incarichi professionali.

Su proposta del Responsabile della S.O.C. Amministrazione Legale e Rapporti con l'Università, Dr.ssa Carla Bini, la quale, con riferimento alla presente procedura, ne attesta la regolarità amministrativa e la legittimità dell'atto.

Ricordato che:

- dal 1 gennaio 2014 al 31 dicembre 2020 è stato attivo il programma della Commissione Europea denominato Programma Horizon 2020, quale strumento di finanziamento della ricerca scientifica e dell'innovazione per progetti di ricerca o azioni volte all'innovazione scientifica e tecnologica che avessero un significativo impatto sulla vita dei cittadini europei;
- la Commissione Europea ha previsto, nell'ambito di Horizon 2020, lo schema ERA-NET COFUND con l'obiettivo di concorrere alla creazione di uno Spazio Europeo della Ricerca (European Research Area) che prevedesse il sostegno a progetti finalizzati alla predisposizione di call transnazionali su specifici temi;
- la Commissione Europea ha approvato, a seguito della propria Call "SC1-HCO-03-2017", Implementing the Strategic Research Agenda on Personalised Medicine, il progetto dal titolo "ERA-Net Cofund in Personalised Medicine – ERA PerMed (Grant Agreement n° 779282)", che ha per capofila l'Istituto De Salud Carlos III – Spagna, di cui la Regione Toscana è partner con il ruolo di Funding Agency come da DGR n. 1310 del 27.11.2018;
- il progetto ERA PerMed ha lo scopo di allineare e collegare la ricerca europea sul tema della Medicina Personalizzata attraverso il lancio di 4 call congiunte, e rinforzare così la collaborazione internazionale tra enti regionali e nazionali
- la Regione Toscana con DGR n. 1402 del 16.11.2020 ha ritenuto di confermare la propria partecipazione, in qualità di Funding Agency, alla Joint Transnational Call 2021 "Multidisciplinary research projects on personalised medicine – Development of clinical support tools for

personalised medicine implementation", investendo una quota di cofinanziamento di € 300.000,00, destinata alle Aziende ed Enti del Servizio Sanitario Regionale e agli enti di ricerca toscani con lo scopo di incentivare la realizzazione di progetti scientifici eccellenti sul

- con DGR n. 1034 del 11.10.2021 ha incrementato i fondi necessari al finanziamento dei 2 progetti toscani in graduatoria e, con atto dirigenziale n. 19492 del 02.11.2021, si è preso atto del finanziamento complessivo dei progetti rinviando a successivo provvedimento l'approvazione dello schema di convenzione da sottoscrivere tra Regione Toscana e i beneficiari, contenente gli impegni e gli obblighi amministrativi necessari a garantire la corretta ed efficace realizzazione del progetto, nonché le linee guida per la rendicontazione.

Dato atto che:

- a seguito della pubblicazione in data 14.12.2012 della Call for Proposal 2021 "Multidisciplinary research projects on personalised medicine – Development of clinical support tools for personalised medicine implementation" (JTC 2021) con la quale sono stati invitati i ricercatori a presentare proposte progettuali, è stato presentato anche il progetto "Implementation of personalised management in nephrotic syndrome PER-NEPH" il cui capofila è l'AOU Meyer – P.I. Prof.ssa Paola Romagnani, e che prevede la partecipazione dell'Università degli Studi di Firenze, del Bellvitge Biomedical Research Institute di L'Hospitalet de Llbregat e dell'University Hospital of the Ludwig-Maximilians University Munich (LMU Klinikum) di Muenchen;
- il costo totale del progetto ammonta a € 1.057.182 dei quali € 698.880,00 richiesti quale contributo di cui € 170.000,00 destinati all'AOU Meyer ed € 130.000,00 all'Università degli Studi di Firenze;
- il progetto di cui sopra è stato ammesso dal Segretariato della JTC 2021 a finanziamento con un contributo massimo di € 300.000,00 e fra i partners del progetto transnazionale, a norma della JTC 2021, deve essere sottoscritto un Consortium Agreement, in fase di predisposizione, al fine di gestire la realizzazione delle attività del progetto, i diritti di proprietà intellettuale e del processo decisionale, per evitare controversie, che potrebbero compromettere il completamento del progetto;
- il progetto ha avuto inizio in data 01.04.2022 ed ha la durata di 36 mesi.

Considerato che, ai fini della corretta ed efficace conduzione del progetto, è prevista la stipula di apposita convenzione fra la Regione Toscana, l'AOU Meyer e l'Università degli Studi di Firenze secondo lo schema approvato con decreto dirigenziale n. 20127 del 18.11.2021 e trasmesso dalla Direzione Sanità, Welfare e Coesione Sociale in data 17.05.2022 (allegato 1 al presente provvedimento a formarne parte integrante e sostanziale).

Ritenuta la necessità ed urgenza di dichiarare il presente provvedimento immediatamente eseguibile al fine di chiedere l'erogazione del 50% del finanziamento regionale a copertura delle attività progettuali iniziate fin dal 1 aprile 2022.

Considerato che il Responsabile del Procedimento, individuato ai sensi della Legge n. 241/1990 nella persona della Dr.ssa Carla Bini sottoscrivendo l'atto attesta che lo stesso, a seguito dell'istruttoria effettuata, nella forma e nella sostanza è legittimo.

Acquisito il parere del Coordinatore dell'Area Tecnico Amministrativa, Dr.ssa Carla Bini, espresso mediante sottoscrizione del presente atto.

Vista la sottoscrizione del Direttore Sanitario e del Direttore Amministrativo, per quanto di competenza, ai sensi dell'art. 3 del Decreto Legislativo n. 229/99.

DELIBERA

Per quanto esposto in narrativa che espressamente si richiama,

1. di prendere atto del progetto "Implementation of personalised management in nephrotic syndrome PER-NEPH", il cui capofila è l'AOU Meyer – P.I. Prof.ssa Paola Romagnani - e che prevede la partecipazione dell'Università degli Studi di Firenze;

2. di dare atto che il progetto PER-NEPH è finanziato dalla Regione Toscana, con un contributo complessivo di € 300.000,00 e che tale importo sarà acquisito ai Bilanci di competenza al conto di ricavo 4101102040 "Contributi da Regione Toscana a destinazione vincolata da quota fondo sanitario regionale indistinto";

3. di rinviare a successivo atto l'approvazione del Consortium Agreement fra i partners del progetto transnazionale, attualmente in fase di predisposizione;

4. di stipulare con la Regione Toscana e l'Università degli Studi di Firenze una convenzione per la realizzazione del progetto, secondo lo schema allegato 1 al presente provvedimento;

5. di dare atto che l'importo destinato all'Università degli Studi di Firenze quale quota parte del contributo regionale è di € 130.000,00, che sarà erogato secondo le modalità indicate nella sopra citata convenzione, con imputazione ai bilanci di competenza;

6. di autorizzare ai sensi dell'art. 3 della convenzione, l'erogazione all'Università degli Studi di Firenze del 50% dell'importo complessivo pari a € 65.000,00 imputandolo al Bilancio 2022 PRCD C05 4202280090 "Costi per contributi Università per attività di ricerca/D*22..... – F.P. N02052203;

7. di dichiarare il presente provvedimento immediatamente eseguibile ai sensi dell'art. 42, comma 4 della L.R.T. n. 40/2005;

8. di trasmettere il presente atto al Collegio Sindacale ai sensi dell'art. 42, comma 2, della L.R.T. n. 40/2005 contemporaneamente all'inoltro all'albo di pubblicità degli atti di questa A.O.U. Meyer.

IL DIRETTORE GENERALE
(Dr. Alberto Zanobini)

IL DIRETTORE SANITARIO
(Dr.ssa Francesca Bellini)

IL DIRETTORE AMMINISTRATIVO
(Dr. Tito Berti)

Regione Toscana
Direzione Sanità, Welfare e Coesione Sociale
Settore Ricerca e investimenti in ambito sanitario

ERA-NET COFUND IN PERSONALISED MEDICINE – ERA PERMED (G.A. N° 779282)
JOINT TRANSNATIONAL CALL 2021

CONVENZIONE PER LA REALIZZAZIONE DEL PROGETTO "Implementation of personalised management in nephrotic syndrome" PER-NEPH

TRA
REGIONE TOSCANA
E
AZIENDA OSPEDALIERO-UNIVERSITARIA A. MEYER
E
UNIVERSITA' DEGLI STUDI DI FIRENZE

La REGIONE TOSCANA con sede in Firenze, Palazzo Strozzi Sacrati, Piazza del Duomo n. 10, C.F. e P. IVA n. 01386030488, rappresentata dalla Dirigente regionale Elisa Nannicini nata a Firenze il 5/10/1971, domiciliata presso la sede dell'Ente, il quale interviene nella sua qualità di Dirigente del Settore "Ricerca e investimenti in ambito sanitario", struttura competente per materia, nominata con decreto n. 8677/2021 ed autorizzata, ai sensi dell'art. 54 della L. R. 13/07/07 n. 38, ad impegnare legalmente e formalmente l'Ente medesimo con il presente atto, il cui schema è stato approvato con D.D n. 20127 del 18.11.2021;

E

L'AZIENDA OSPEDALIERO-UNIVERSITARIA A. MEYER, (di seguito denominato 1° Beneficiario toscano", con sede legale in Viale Pieraccini 24, 50134 Firenze C.F. e P. I. 02175680483, rappresentata dal Direttore Generale Alberto Zanobini, nato a Montevarchi (AR) il 26/09/1965, in qualità di legale rappresentante pro tempore, domiciliato per il presente atto presso la sede dell'ente;

E

L'UNIVERSITA' DEGLI STUDI DI FIRENZE, Dipartimento di Scienze Biomediche Sperimentali e Cliniche "Mario Serio"(di seguito denominato "2° Beneficiario toscano"), con sede legale in Firenze, Piazza San Marco, 4 – 50121 Firenze, C.F. e P. I. 01279680480, rappresentata dal Prof. Andrea Galli, nato a Firenze il 24/06/1966, in qualità di Direttore del Dipartimento di Scienze Biomediche Sperimentali e Cliniche "Mario Serio" - Procuratore speciale del Rettore dell'Università degli Studi di Firenze, domiciliato per il presente atto presso la sede dell'ente;

PREMESSO CHE

- la Commissione Europea, nell'ambito del Programma Horizon 2020, ha approvato, a seguito della Call "SC1-HCO-03-2017 - Implementing the Strategic Research Agenda on Personalised Medicine", il progetto dal titolo "ERA-Net Cofund in Personalised Medicine –

ERA PerMed (Grant Agreement n° 779282)", che ha per capofila l'Instituto de Salud Carlos III – Spagna;

- la Regione Toscana:
  - con la Delibera della Giunta Regionale n. 1310 del 27 novembre 2018 ha aderito, in qualità di Funding Agency, al progetto "ERA-Net Cofund in Personalised Medicine ERA PerMed;
  - con la Delibera della Giunta Regionale n. 1402 del 16.11.2020 ha stabilito di partecipare, in qualità di Funding Agency, alla Joint Transnational Call 2021 "Multidisciplinary research projects on personalised medicine – Development of clinical support tools for personalised medicine implementation", mettendo a disposizione una quota di cofinanziamento stimata in € 300.000,00;
  - con la Delibera della Giunta Regionale n. 1034 del 11 ottobre 2021 ha integrato le risorse messe a disposizione dalla DGR 1402/2020;
- il 14 dicembre 2020 è stata pubblicata la Call for Proposals 2021 "Multidisciplinary research projects on personalised medicine – Development of clinical support tools for personalised medicine implementation" (JTC 2021);
- fra le proposte valutate nella fase finale risulta il progetto "Implementation of personalised management in nephrotic syndrome - PER-NEPH" che come capofila del progetto transnazionale l'Azienda Ospedaliera-Universitaria Meyer e a cui partecipa anche l'Università degli Studi di Firenze, con una richiesta totale a Regione Toscana di euro 300.000,00 Principal Investigator prof.ssa Paola Romagnani;
- a seguito dell'espletamento delle fasi istruttorie, con email del 13 ottobre 2021, il Segretariato della JTC2021 ha comunicato la graduatoria definitiva con i progetti ammessi e non ammessi a finanziamento;
- il Progetto denominato "Implementation of personalised management in nephrotic syndrome - PER-NEPH", numero CUP G15F21001060002 (CUP MASTER AOU Meyer) B55F21005510002 (CUP UNIFI), (d'ora in avanti denominato "Progetto"), risulta tra i progetti finanziati;
- l'ammissione a contributo è condizionata alla verifica con esito positivo nonché al mantenimento dei requisiti previsti e dichiarati in sede di presentazione della domanda di partecipazione e ad ogni altra condizione necessaria prevista dalla normativa vigente e dal Bando;

VISTA

la normativa di riferimento ed, in particolare:

- la legge regionale n. 40 del 24 febbraio 2005 e s.m.,
- il Programma regionale di sviluppo 2016-2020 approvato dal Consiglio regionale con la risoluzione n. 47 del 15 marzo 2017,
- il Documento di Economia e Finanza Regionale (DEFR) 2021 approvato con Deliberazione del Consiglio Regionale n. 49 del 30 luglio 2020 e la successiva Integrazione alla Nota di Aggiornamento di cui alla DCR n. 85 del 30 luglio 2021,
- il "Piano Sanitario e Sociale Integrato Regionale 2018-2020"approvato con Deliberazione del Consiglio Regionale n. 73 del 09/10/2019,
- la "Strategia di Ricerca e Innovazione per la Smart Specialisation in Toscana" (DGR 1018/2014),
- la delibera della Giunta Regionale n. 1310 del 27 novembre 2018,
- la Delibera della Giunta Regionale n. 1402 del 16.11.2020,

- il decreto dirigenziale n. 18676 del 19 novembre 2020,
- la Delibera della Giunta Regionale n. 1034 del 11 ottobre 2021,
- il decreto dirigenziale n.19492 del 2 novembre 2021,
- il decreto dirigenziale n. 20127 del 18.11.2021,
- il decreto dirigenziale n. 20197 del 19 novembre 2021,
- il decreto dirigenziale n. 20341 del 22 novembre 2021;

TUTTO CIÒ PREMESSO

i contraenti, come sopra costituiti, convengono e stipulano quanto segue:

Art. 1 – Oggetto

La presente Convenzione ha per oggetto la realizzazione delle attività del Progetto "Implementation of personalised management in nephrotic syndrome" - Acronimo "PER-NEPH", con capofila l'AOU Meyer e con la responsabilità scientifica della prof. Paola Romagnani,

Art. 2 – Durata

La presente Convenzione - sottoscritta ai sensi dell'art. 15 della L. n. 241/1990 e ss.mm.ii. - ha decorrenza dalla data di apposizione dell'ultima firma della stessa e ha validità fino ai cinque anni successivi alla rendicontazione del progetto realizzato.
La data di avvio del progetto è il 1° aprile 2022 come da comunicazione del 1° beneficiario toscano.
Il progetto deve essere completato entro 36 mesi dalla data di avvio del progetto.
Potrà essere concessa una proroga delle attività del Progetto per un periodo massimo di 6 mesi, previa istanza del 1° beneficiario toscano e comunque in accordo con il partenariato del progetto transnazionale.
La richiesta di proroga deve essere motivata e corredata da una relazione sullo stato di avanzamento del progetto e della spesa.

Art. 3 – Obblighi della Regione Toscana

La Regione Toscana si impegna a corrispondere al 1° beneficiario toscano, nelle forme e modalità stabilite dalla presente Convenzione, un contributo fino ad un massimo di euro 300.000,00 (trecentomila) nella forma del contributo a fondo perduto.
Il contributo è concesso con le seguenti modalità:

1. in anticipazione fino al 50% del totale del contributo; la domanda di anticipo deve essere presentata direttamente a Regione Toscana entro 1 mese dalla data di sottoscrizione della presente convenzione;
2. per stato avanzamento lavori (d'ora in avanti "SAL"), in due rate pari al 20% (proporzionalmente alle spese ammissibili rendicontate), da presentare entro 45 giorni dalla data di conclusione del:
    a) primo periodo di rendicontazione (12 mesi dalla data di avvio del progetto)
    b) secondo periodo di rendicontazione (24 mesi dalla data di avvio del progetto)

    La domanda a titolo di SAL deve essere presentata dal 1° beneficiario toscano a Regione Toscana unitamente alla rendicontazione dei costi totali sostenuti e si compone di:
    - relazione tecnica intermedia sullo stato di avanzamento del progetto;
    - fatture o documenti contabili di equivalente valore probatorio, completi di documentazione relativa al pagamento, rappresentata dalla ricevuta contabile del bonifico o altro documento (bancario) relativo allo strumento di pagamento prescelto, in cui sia documentato il sottostante movimento finanziario, con

indicazione nella causale degli estremi del titolo di spesa a cui il pagamento si riferisce (normativa antiriciclaggio D.Lgs. 231/07).

La mancata rendicontazione delle spese e/o la mancata presentazione della relazione tecnica intermedia sarà considerata come rinuncia implicita dei beneficiari alla realizzazione del progetto e, trascorsi ulteriori 30 giorni dalla scadenza dei termini, determinerà la revoca dell'intero contributo.

La quota del SAL sarà erogata solo nel caso in cui sia il controllo sulla rendicontazione presentata che la valutazione sulla relazione intermedia sullo stato di avanzamento del progetto abbiano avuto esito positivo.

3. a saldo (36 mesi dalla data di avvio del progetto), pari alla quota restante di contributo; l'esatto ammontare del contributo da erogare verrà determinato sulla base delle spese ritenute ammissibili di cui alle "Linee guida per la rendicontazione".

   La richiesta di pagamento saldo deve essere presentata dal 1° beneficiario toscano, entro 45 giorni dalla conclusione del terzo periodo di rendicontazione (36 mesi dalla data di avvio del progetto o entro nuovo termine concesso dall'Amministrazione a seguito di proroga), unitamente alla relazione tecnica conclusiva.

   Il saldo sarà erogato solo nel caso in cui sia il controllo sulla rendicontazione presentata che la valutazione sulla relazione finale del progetto abbiano avuto esito positivo.

Art. 4 – Obblighi dei beneficiari

Nel rispetto degli obblighi della normativa di riferimento e della presente Convenzione, i beneficiari si impegnano a:

1. realizzare il progetto entro il termine indicato nella proposta progettuale, conformemente all'oggetto, agli obiettivi e ai risultati attesi della ricerca contenuti nel progetto approvato;
2. comunicare, anticipatamente e tempestivamente, tutte le modifiche inerenti al progetto approvato;
3. rendicontare le spese effettivamente sostenute per la realizzazione del progetto, fornendo le relazioni tecniche per ciascun stato di avanzamento, al diciottesimo ed al trentaseiesimo mese dalla data di avvio progetto;
4. garantire la conservazione fino al quinto anno successivo all'erogazione del saldo della documentazione scientifica e contabile inerente la sua realizzazione;
5. consentire ai funzionari della Regione Toscana o a soggetti da essa incaricati, lo svolgimento di controlli o ispezioni;
6. rispettare gli obblighi di informazione e pubblicità previsti dal Bando.

   I beneficiari autorizzano la Regione Toscana a pubblicare, anche per estratto, le relazioni intermedia e finale del progetto di ricerca e le relative valutazioni, nel rispetto della tutela dei dati personali e nel rispetto della tutela dei diritti di proprietà intellettuale inerenti ai risultati del progetto.
7. rispettare il divieto di cumulo impegnandosi per il futuro a non cumulare altri finanziamenti per le stesse attività progettuali;
8. mantenere i requisiti di ammissibilità per tutta la durata del progetto e comunque fino all'istanza di erogazione del saldo;
9. comunicare tempestivamente al Responsabile del procedimento, mediante PEC all'indirizzo regionetoscana@postacert.toscana.it l'eventuale rinuncia al contributo.

Art. 5 Spese ammissibili e rendicontazione

Le spese ammissibili sono quelle indicate nell'Allegato A al decreto n.18676/2020 – Criteri di ammissibilità, purché effettivamente sostenute dai beneficiari tra la data di avvio del progetto di cui all'articolo 2 della presente Convenzione ed i 36 mesi successivi, salvo eventuale proroga.
La rendicontazione delle spese sostenute deve essere presentata secondo le modalità stabilite nelle "Linee guida per la rendicontazione".

Art. 6 - Erogazione del contributo

L'erogazione del contributo è effettuata al 1° beneficiario toscano secondo le modalità indicate nelle Linee guida per la rendicontazione.

Art. 7 - Divieto di cumulo

Il contributo di cui al Bando ed alla presente Convenzione non è cumulabile con altri finanziamenti, contributi o incentivi pubblici concessi per le stesse iniziative ed aventi ad oggetto le stesse spese.

Art. 8 – Valutazione intermedia e finale

Il Progetto è sottoposto a valutazione annuale e finale dei risultati conseguiti, secondo le modalità previste dal Segretariato dell'ERA-Net Cofund in Personalised Medicine - ERA PerMed .

Le suddette valutazioni sono effettuate sulla base delle informazioni fornite nelle relazioni tecniche annuali e finali, allegate alle relative rendicontazioni, e sono dirette ad accertare:

- la coerenza dell'oggetto, degli obiettivi e dei risultati conseguiti dal progetto realizzato rispetto a quello ammesso a finanziamento;
- per le valutazioni intermedie, la potenzialità del progetto di perseguire gli obiettivi dichiarati in fase di presentazione della domanda che non sono stati ancora raggiunti;
- la congruità delle spese sostenute, il rispetto del cronoprogramma e degli altri elementi di progetto approvato.

Il 1° beneficiario toscano dovrà inviare annualmente, in parallelo con la procedura centralizzata del Joint Call Secretariat (JCS), una copia della relazione tecnica (progress report) e il risultato della valutazione ricevuta dal JCS

Le rendicontazioni finanziarie annuali e finali devono essere elaborate conformemente alle indicazioni fornite dall'Amministrazione regionale e secondo l'apposito modello allegato alle Linee Guida per la Rendicontazione ed inviate con la copia del progress report e della sua valutazione.
Le relazioni tecniche e le rendicontazioni finanziarie dovranno essere trasmesse - entro 45 giorni dalla scadenza rispettivamente del dodicesimo, ventiquattresimo e del trentaseiesimo mese dall'inizio del progetto (o entro nuovo termine concesso dall'Amministrazione a seguito di proroga) - all'indirizzo pec regionetoscana@postacert.toscana.it e contestualmente caricate in upload sul Sistema Unificato di Monitoraggio dei progetti in Toscana" (MoniToscana) all'indirizzo https://web.rete.toscana.it/monitoscana.

Eventuali difformità, fra risultati attesi e risultati conseguiti, dovranno essere adeguatamente motivate.
Il 1° beneficiario toscano dovrà fornire tutte le informazioni e le documentazioni finanziarie, tecniche e amministrative del Progetto richieste dalla Regione; dovrà inoltre fornire le attestazioni necessarie per la verifica del possesso e del mantenimento dei requisiti di cui alla Call ed eventuali integrazioni, entro un termine massimo di 10 giorni dalla richiesta, se non diversamente stabilito.
La mancata trasmissione delle relazioni intermedia e finale sullo stato di attuazione del progetto, la

mancata motivazione di eventuali difformità rispetto al progetto approvato o la mancata rispondenza delle relazioni a quanto indicato nel bando comportano la sospensione delle erogazioni e l'eventuale revoca del contributo.
La Regione Toscana si riserva il diritto di richiedere, in qualsiasi momento, al 1° beneficiario toscano una relazione relativa allo stato di avanzamento del progetto.

Art. 9 - Proprietà intellettuale e diffusione dei risultati

I risultati, le invenzioni, il knowhow, gli eventuali dati o informazioni, compresi gli eventuali software realizzati ad hoc per la ricerca, brevettabili o meno, ed ogni altro diritto di proprietà intellettuale raggiunto o realizzato nel corso dell'attività di ricerca inerente al progetto (foreground, knowledge), appartengono congiuntamente ai beneficiari del progetto ed agli altri partner di progetto, in misura proporzionale al relativo contributo inventivo. Il beneficiario/i e agli altri partner di progetto coinvolti stipulano il Consortium Agreement atto a definire l'effettiva ripartizione e le condizioni di esercizio di tale proprietà.
I diritti di proprietà intellettuale già sviluppati, al momento della stipula della convenzione (inizio del progetto), dai soggetti beneficiari e dagli altri partner coinvolti nell'attività di ricerca (background, pre-existing know-how) rimangono di loro propria titolarità.
Le pubblicazioni e ogni altro mezzo di divulgazione dei risultati derivanti dal progetto, dovranno esporre il logo UE e di Regione Toscana e riportare la seguente dicitura: "This project has received funding from the European Union's Horizon 2020 research and innovation programme and from Tuscany Region under theERA-Net Cofund in Personalised Medicine ERA PerMed (GA n° 779282)".
I beneficiari autorizzano la Regione Toscana a pubblicare, anche per estratto, le relazioni intermedie e finali del progetto di ricerca e le relative valutazioni, nel rispetto della tutela dei dati personali e nel rispetto della tutela dei diritti di proprietà intellettuale inerenti ai risultati del progetto.

Art. 10 - Ispezioni e controlli

La Regione Toscana si riserva di effettuare, in qualsiasi momento, ispezioni documentali presso i soggetti beneficiari allo scopo di verificare lo stato di esecuzione, il rispetto degli obblighi previsti dalla normativa vigente e dal bando e la veridicità delle informazioni fornite dai beneficiari.

Art. 11 – Sospensione delle erogazioni e revoche

È disposta la sospensione del contributo qualora emerga la mancata o ritardata attuazione del progetto e delle relative spese e l'inottemperanza agli obblighi di cui all'art. 4 della presente convenzione.
Il contributo sarà revocato nei seguenti casi:

a) rinuncia dei beneficiari;
b) mancato rispetto degli obblighi di cui all'art. 4 della presente convenzione; per gli obblighi di cui all'art. 4 punto 2, la Regione Toscana si riserva, prima di procedere a revoca, una valutazione a proprio insindacabile giudizio della rilevanza del mancato rispetto;
c) inadempienze dei beneficiari rispetto ai requisiti soggettivi ed oggettivi di cui all'Allegato A al decreto n. 18676/2020 – Criteri di ammissibilità, nonché tutte le altre violazioni della normativa di riferimento;
d) mancata attuazione degli adempimenti successivi all'ammissione a finanziamento;

La Regione Toscana, qualora si verifichino le circostanze che danno luogo alla revoca del contributo, comunica al 1° beneficiario toscano l'avvio del procedimento con indicazioni relative all'oggetto del procedimento promosso, all'ufficio e alla persona responsabile del procedimento,

presso i quali si può prendere visione degli atti, e assegna ai destinatari un termine di 30 giorni, decorrente dalla ricezione della comunicazione stessa, per presentare eventuali controdeduzioni o scritti difensivi, redatti in carta libera, nonché altra documentazione ritenuta idonea. La presentazione degli scritti e della documentazione di cui sopra deve avvenire con la stessa modalità utilizzata dalla Regione Toscana per la notifica dell'avvio del procedimento.
I contributi indebitamente percepiti dovranno essere restituiti dai beneficiari interessati.

Art. 12 - Difforme e/o parziale realizzazione del progetto

Costituiscono difforme e/o parziale realizzazione del progetto la:

1. non completa/parziale realizzazione del progetto e/o non corretta rendicontazione finale del progetto;
2. rideterminazione del contributo per irregolarità riscontrate a seguito di controlli a qualsiasi titolo effettuati, per le quali non si procede a revoca totale.

Nei casi di cui al comma precedente la Regione Toscana, previo contraddittorio con il 1° beneficiario toscano, potrà procedere alla revoca parziale dell'agevolazione.
La difforme o parziale realizzazione del progetto costituisce ipotesi di adempimento difforme/parziale della Convenzione e, come tale sarà sottoposta all'approvazione del Dirigente responsabile del settore Ricerca e investimenti in ambito sanitario.
Nel caso in cui vi sia stata erogazione da parte della Regione Toscana, con il provvedimento di revoca è disposta la restituzione delle somme erogate, maggiorate degli interessi maturati al Tasso Ufficiale di Riferimento (d'ora in avanti "TUR").
Nel caso in cui alla data della revoca parziale le erogazioni siano in corso, l'ammontare da recuperare sarà detratto a valere sull'erogazione ancora da effettuare. Nel caso in cui le erogazioni ancora da effettuare risultino di ammontare inferiore a quello da recuperare o nel caso in cui si sia già provveduto all'erogazione a saldo, sarà avviata una procedura di recupero (anche coattivo secondo quanto disposto dalla legge di contabilità della Regione e dal regolamento di attuazione) nei confronti dei beneficiari interessati.

Art. 13 - Trattamento dei dati personali

I dati dei quali la Regione Toscana entra in possesso a seguito della partecipazione alla Joint Transnational Call 2021 – ERA PerMed e per la sottoscrizione della presente Convenzione, verranno trattati nel rispetto della vigente normativa di cui al D.Lgs. 196/2003 e successive modifiche ed integrazioni ed al GDPR (Regolamento UE 2016/679).
A tal fine si fa presente che:

- La Regione Toscana- Giunta regionale è il titolare del trattamento (dati di contatto: P.zza Duomo 10 - 50122 Firenze; regionetoscana@postacert.toscana.it)
- Il conferimento dei dati, che saranno trattati dal personale autorizzato con modalità manuale e informatizzata, è obbligatorio ed il loro mancato conferimento preclude i benefici derivanti dalla Call e dalla presente Convenzione. I dati raccolti non saranno oggetto di comunicazione a terzi, se non per obbligo di legge.
- I dati saranno conservati presso gli uffici del Responsabile del procedimento (Settore Ricerca e investimenti in ambito sanitario) per il tempo necessario alla conclusione del procedimento stesso, saranno poi conservati in conformità alle norme sulla conservazione della documentazione amministrativa.
- L'interessato ha il diritto di accedere ai dati personali che lo riguardano, di chiederne la rettifica, la limitazione o la cancellazione se incompleti, erronei o raccolti in violazione della

legge, nonché di opporsi al loro trattamento per motivi legittimi rivolgendo le richieste al Responsabile della protezione dei dati (*urp_*dpo@regione.toscana.it*)*.

- L'interessato può inoltre proporre reclamo al Garante per la protezione dei dati personali, seguendo le indicazioni riportate sul sito dell'Autorità (http://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/4535524)

Art. 14- Registrazione e oneri fiscali

La presente Convenzione sarà registrata solo in caso d'uso ai sensi del D.P.R. n. 131/1986 a cura e spese della parte richiedente.
Ogni altra spesa relativa alla presente Convenzione, in qualunque tempo e a qualsiasi titolo accertate, è a carico dei beneficiari.

Art. 15 - Foro competente

Per qualsiasi controversia derivante o connessa alla presente Convenzione, ove la Regione Toscana sia attore o convenuto, è competente il Foro di Firenze, con espressa rinuncia a qualsiasi altro.

Art. 16 - Norme di rinvio

Per tutto quanto non espressamente previsto dalla presente Convenzione e dalla documentazione della Joint Transnational Call 2021, si richiamano le norme comunitarie, nazionali e regionali vigenti in materia.

LETTO, APPROVATO E SOTTOSCRITTO

REGIONE TOSCANA
La dirigente

AOU MEYER
Il legale rappresentante

Università degli Studi di Firenze
Il legale rappresentante

ALLEGATI:

1) Scheda tecnica di Progetto con Piano finanziario di Progetto.

ERAPerMed

JOINT TRANSNATIONAL CALL FOR PROPOSALS (2021) FOR

"MULTIDISCIPLINARY RESEARCH PROJECTS ON PERSONALISED MEDICINE – DEVELOPMENT OF CLINICAL SUPPORT TOOLS FOR PERSONALISED MEDICINE IMPLEMENTATION"

ERAPerMed

FULL-PROPOSAL APPLICATION FORM

Please note:

- **Proposals that do not meet the national/regional eligibility criteria and requirements will be declined without further review.**
- **All fields must be completed using "Calibri font, size 11" characters, single-spaced.**
- **Incomplete proposals (proposal missing any sections), proposals using a different format or exceeding length limitations of any sections will be rejected without further review.**
- **In case of inconsistency between the information registered in the submission tool and the information included in the PDF of this application form, the information registered in the submission tool shall prevail.**
- **Refer to the "GUIDELINES FOR APPLICANTS" for information about the proposal structure.**
- **Once completed, the full-proposal must be converted in a single PDF document before being uploaded to the submission website.**

CHECKLIST FOR THE COORDINATOR:

In order to make sure that your proposal will be eligible to this call, please collect the information required (on the "Call Text", "Guidelines for applicants" and through your contact point) to tick all the sections below before starting to complete this application form.

- **General conditions:**

X The project proposal addresses the **AIM/s** of the call.

X The project proposal addresses **the modules 1B "Clinical Research", 2 "Towards application in health care" and 3B "Ethical, Legal and Social Aspects".**

X I am aware of the **regional/national requirements** of the corresponding funding organisations**.**

X The pre-proposal was positively evaluated and I have been invited to submit a full-proposal.

- **Composition of the consortium:**

X The project proposal involves at least 3 eligible research groups from at least 3 different countries participating in the second ERA PerMed joint transnational call.

X The project coordinator is eligible to be funded by one of the participating funding organisations.

X The project consortium does not include more than two partners from the same country participating in the call (see "Guidelines for Applicants" for specific regional/national regulations).

X The project consortium includes at least two partners from two different EU Member States or Associated Countries.

X The project proposal involves no more than 6 partners.

☐ The project proposal involves no more than 7 partners after inclusion of a partner from an underrepresented country (**:ANID (Chile), MSR (Croatia), SMWK (Saxony); VIAA (Latvia) and TUBITAK (Turkey)**

☐ The project proposal involves no more than one research group with its own funding.

☐ If a research group with its own funding is part of the consortium, the respective partner is indicated as a full partner in this proposal template.

- **Eligibility of consortium partners:**

X I have checked that no partner of this consortium is a member of the ERA PerMed Network Steering Committee (NSC), Peer Review Panel (PRP), Call Steering Committee (CSC) or Call Advisory Board.

X I have checked that partners involved in the project proposal and requesting budget are eligible to receive funding from their funding organization.

☐ For the partner participating with its own funding, a signed (written) statement is uploaded with this form on the PT-online, declaring that it will be able to run the project with its own resources.

GENERAL INFORMATION

Project title

Implementation of personalised management in nephrotic syndrome

Acronym (max. 15 characters)

PER-NEPH

Project duration (months)

36

Total project costs (€)*

1,057,182

Total requested budget (€)*

698,880

Please make sure that the same figures are entered in the sections that need to be completed online (PT-outline submission tool) and in the financial overview in section 5 of the full-proposal form. Thousand separators and whole numbers should be used only (e.g. 200,000).

1.1 PROPOSAL CLASSIFICATION

Please tick the appropriate boxes to specify the category of your application.

Each proposal MUST address the modules 1B "Clinical Research", 2 "Towards application in health care" and 3B "Ethical, Legal and Social Aspects".

To address a module/research area adequately, there has to be a dedicated work package in the work plan with a topic fitting to the module. In addition, the partner responsible for the respective work package needs to have the appropriate expertise.

Please indicate in the table below which project partner is involved in which module. Only those modules with a dedicated task for the respective partner should be indicated. Please take into account that some national/regional funding organisations can fund only a subset of modules.

Please indicate the work package number for each module included in the proposal.

Module	1A	1B	2	3A	3B
Coordinator	x	x	x	x	x
Partner 1	x	x	x		
Partner 2		x	x	x	x
Partner 3		x	x		x
WP number	3	1,2	1,2	4	4

1.2 KEYWORDS (FROM 5 UP TO 7)

Please list from 5 to 7 keywords describing your proposal.

Nephrotic syndrome, whole exome sequencing, podocytopathies, genetic testing, relapse

1.3 SCIENTIFIC ABSTRACT (MAX. 2,000 CHARACTERS, INCLUDING SPACES)

Please give a comprehensive and readable summary of the most important aims and methods of the project. Please note that if the project is selected for funding this abstract will be published in the newsletter and on the funding organisations' websites.

Nephrotic syndrome in children and young adults is a frequent medical problem of very diverse pathophysiology and prognosis. Current diagnostic algorithms fail to avoid under- and overtreatment of patients with toxic drugs as defining the underlying cause is frequently difficult. We have developed a diagnostic algorithm of stratifying patients through advanced genetic testing, reverse phenotyping, and personalised disease models. This can double the current diagnostic rate in patients not responding to first line therapy and to predict disease relapse in those that progress to end stage kidney disease and have to undergo kidney transplant.

The aims of this project are to:

1. Implementation of this diagnostic algorithm in selected European sites by a) selecting patients for a personalised genetic diagnosis, b) whole exome sequencing and bioinformatic prioritization of potentially pathogenic variants, c) validating genotype-phenotype correlation for a personalised diagnosis, and d) personalising the assessment of variants of unknown significance by functional studies with patient urine-derived renal progenitors and 3D organ-on-a-chip disease models.

2. Personalising the assessment of non-genetic forms and of relapse after transplant by a) identifying patients negative to the genetic testing, b) assessing patients with proteinuria relapse after kidney transplant, c) personalising the detection of immunologic factors by using STED super-resolution microscopy and d) personalising the detection of circulatory permeability factors by using a 3D organ-on-a-chip model system.

3. Assessing the cost-effectiveness as well as clinical, ethical, and legal consequences of the proposed algorithm by a) a multicentre model-based cost-utility analysis of the proposed algorithm and by assessing the b) clinical, c) ethical, and d) legal consequences in close conjunction with the study participants and the respective patient organisations by standardised questionnaire tools.

2. PROJECT CONSORTIUM

For each of the partners *participating in the project (**also those using with their own funding**), please fill in the following table.*

2.1. COORDINATOR

Last Name	Romagnani
First Name	Paola
Gender	Female
Title	Prof. Dr. med
Institution	Meyer Children's Hospital
Type of entity	☐ Academia (research teams working in universities, other higher education institutions or research institutes) ☒ Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) ☐ Non-profit private partner ☐ For-profit private partner
Department	Nephrology Unit
Position	Head of Nephrology Unit
Address	Viale Pieraccini 24
Postal Code	50139
City	Florence
Country/Region	Italy
Relevant funding organisation	Tuscany region
Phone	+39 055 5662562
Fax	
E-mail	paola.romagnani@meyer.it; paola.romagnani@unifi.it
Other information[1]	
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	Francesca Becherucci, Staff Physician, Meyer Children's Hospital
	Rosangela Artuso, Staff Biologist, Meyer Children's Hospital

[1] **Industry: Additional information** (such as VAT number, turnover, balance sheet) might be requested by your regional/national agency. Please check therefore the "Guidelines for Applicants". If no additional information is requested by your regional/national funding organisation, please write "none".

2.2. PROJECT PARTNER 1

Last Name	Lazzeri
First Name	Elena
Gender	Female
Title	Ph.D
Institution	University of Florence
Type of entity	☒ Academia (research teams working in universities, other higher education institutions or research institutes) ☐ Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) ☐ Non-profit private partner ☐ For-profit private partner
Department	Department of Clinical and Experimental Biomedical Sciences
Position	Associate Professor
Address	Viale Pieraccini 6
Postal Code	50139
City	Florence
Country/Region	Italy
Relevant funding organisation (if no funding is requested, please write "none") [1]	Tuscany region
Phone	+39 055 2758165
Fax	
E-mail	elena.lazzeri@unifi.it
Other information[2]	
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	Lasagni Laura, Associate Professor, Department of Clinical and Experimental Biomedical Sciences, University of Florence
	Maria Lucia Angelotti, Technician, Department of Clinical and Experimental Biomedical Sciences, University of Florence

[1] If no funding is requested, a signed statement has to be enclosed declaring in advance that this partner will run the project with its own resources.

[2] **Industry: Additional information** (such as VAT number, turnover, balance sheet) might be requested by your regional/national agency. Please check therefore the "Guidelines for Applicants". If no additional information is requested by your regional/national funding organisation, please write "none".

2.3. PROJECT PARTNER 2

Last Name	Cruzado
First Name	Josep Maria
Gender	Male
Title	Prof. Dr. med.
Institution	Bellvitge Biomedical Research Institute (IDIBELL)
Type of entity	☐ Academia (research teams working in universities, other higher education institutions or research institutes) ☒ Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) ☐ Non-profit private partner ☐ For-profit private partner
Department	Hospital of Bellvitge , Nephrology
Position	Head of Nephrology Department
Address	Feixa LLarga s/n
Postal Code	08907
City	L'Hospitalet de Llobregat
Country/Region	Spain/Catalonia
Relevant funding organisation (if no funding is requested, please write "none") [1]	Health Department, Catalonia Government (DS-CAT)
Phone	+34-93-2607604
Fax	+34-93-2607607
E-mail	jmcruzado@bellvitgehospital.cat
Other information[2]	
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	Dr Anna Manonelles, Nephrologist, Kidney Transplant Unit, Nephrology Department, Hospital of Bellvitge
	Dr Anna Sola, Principal Investigator, Nephrology and Kidney Transplantation Research Group, IDIBELL

[1] If no funding is requested, a signed statement has to be enclosed declaring in advance that this partner will run the project with its own resources.

[2] **Industry: Additional information** (such as VAT number, turnover, balance sheet) might be requested by your regional/national agency. Please check therefore the "Guidelines for Applicants". If no additional information is requested by your regional/national funding organisation, please write "none".

2.4. PROJECT PARTNER 3

Last Name	Anders
First Name	Hans-Joachim
Gender	Male
Title	Prof. Dr. med.
Institution	University Hospital of the Ludwig-Maximilians University Munich (LMU Klinikum)
Type of entity	☒ Academia (research teams working in universities, other higher education institutions or research institutes) ☐ Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) ☐ Non-profit private partner ☐ For-profit private partner
Department	Division of Nephrology, Department of Internal Medicine IV
Position	Head of Nephrology Department, Inner City Campus
Address	Ziemssenstr. 1
Postal Code	80336
City	Muenchen
Country/Region	Germany
Relevant funding organisation (if no funding is requested, please write "none") [1]	BMBF
Phone	+49-89-440053583
Fax	+49-89-440053379
E-mail	hjanders@med.uni-muenchen.de
Other information[2]	
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	PD Dr. med. Lange-Sperandio, Bärbel, Head of Pediatric Nephrology, LMU Klinikum

[1] If no funding is requested, a signed statement has to be enclosed declaring in advance that this partner will run the project with its own resources.

[2] **Industry: Additional information** (such as VAT number, turnover, balance sheet) might be requested by your regional/national agency. Please check therefore the "Guidelines for Applicants". If no additional information is requested by your regional/national funding organisation, please write "none".

3. PROJECT DESCRIPTION

3.1. PROPOSED WORK (MAX. 3 PAGES)

The following five subsections MUST be completed in these three pages:

1. *Justify how the proposal fits in the scope of the call;*

The clinical impact of nephrotic syndrome (NS) together with heterogeneity of genetic and non-genetic causes among patients with different prognosis and response to treatments[1] urgently requires a personalised approach. The proposed diagnostic algorithm, preliminarily implemented in the center directed by the coordinator, permits doubling of the rate of genetic diagnosis making use of whole exome sequencing (WES)[2], personalised disease models[3,4], and advanced multidisciplinary phenotyping of patients[2,5].This diagnostic process reduces the risk of inappropriate treatments and optimizes the choice of drugs[2]. It extends the lifespan of patients, increases the quality of clinical practice, improves the quality of life of patients, and reduces costs for the public health system. The proposal strictly matches the purpose of the Call to create and implement precision medicine models that will include genetic and accurate phenotypic information with aim to create innovative diagnostic and therapeutic strategies focused on the individual features of patients affected by NS. This will imply a significant impact on clinical decisions and health outcomes. The EraPerMed program could be an opportunity to roll out this diagnostic process across Europe, thanks to the involvement of leading centers in the field in Germany and Spain. This network will accelerate the implementation strategy across Europe.

2. *Explain the Personalised Medicine dimension of the proposed work and its added value to the scientific question addressed in the proposal;*

The proposal focuses on implementation of a diagnostic algorithm for the management of patients with NS taking advantage from personalised diagnostic strategies. State-of-the art research techniques, such as 3D organ-on-a-chip disease models[6] using renal progenitors (RPC) obtained from the urine of patients[3], STED super-resolution microscopy of human kidneys[7], or single cell RNA sequencing (scRNAseq)[6] to identify biomarkers for patient stratification will introduce a significant technological innovation in the clinical diagnosis and management of NS. Upon successful application in the coordinator hospital, the public health system of Tuscany previously funded a project on implementing this diagnostic algorithm on all patients with NS of the Tuscany region. Application of this algorithm reduced the risk of inappropriate treatments, optimized the choice of drugs[2], improved the quality of life of patients, and reduced costs for the public health system. We propose that application of this algorithm across Europe can accelerate the translation between mechanistic insights and individualized treatment and improve the performance of diagnosis, prediction, and monitoring of therapeutic response.

3. *Background, present state of the art and preliminary results obtained by the consortium members;*

Background: NS is a frequent and often severe medical problem of diverse pathophysiology and prognosis that develops from a severe and diffuse injury to the crucial cell constituents of the glomerular filtration barrier, the podocytes[1]. Injuries include extrinsic (infections, drugs) and intrinsic (autoimmunity, genetic disorders, metabolic disease) causes. **State-of-the art:** Diagnosis and management of the underlying cause of NS is difficult and not standardized. Excluding those patients that responds quickly to high-dose steroid treatment, a part of patients are not responders and thus, receive frequently extended high-dose steroid therapy and a series of other immunosuppressant drugs, which can potentially have deleterious side effects[1]. Genetic testing has developed as a powerful tool to identify patients that will not benefit from immunosuppressive drugs and to avoid unnecessary treatment-related morbidity and costs. In addition, genetic testing can sometimes even enable identification of patients that will benefit from specific treatments (for ex. patients with pathogenetic mutations in coenzyme Q10 biosynthesis may respond to oral coenzyme Q10 supplementation)[1,8,9]. Genetic testing for pathogenic variants in genes involved in

podocyte structure and function evolved as a new standard to identify monogenic kidney disorders causing NS, e.g. podocyte-related or syndromal non-podocyte-related genes namely collagenopathies[1]. On the other hand, patients negative to genetic testing frequently benefit from immunosuppressive drugs suggesting a role of unknown immunological or circulating permeability factors[1]. Such patients can develop a relapse after kidney transplantion[10,11]. This causal diversity implies the importance for a personalised approach. Only, a correct diagnosis made early can reduce morbidity, risk of inappropriate treatments with serious side effects, progression to kidney failure and the associated high costs and the severe impact on quality of life.

Preliminary results: The coordinator and partner1 developed an integrated diagnostic algorithm that permits a successful personalised genetic diagnosis in up to 60% of children and young adults with steroid-resistant NS (SRNS)[2,5].The algorithm is based on: 1. Selection of patients for genetic testing; 2.WES analysis followed by an *in silico* analysis of an extended panel of genes associated with podocytopathies and other genetic syndromes reported to occasionally present with isolated SRNS (that is, as phenocopies of podocytopathies); 3. Genotype-phenotype correlation and reverse phenotyping of the patient and his/her family; 4. Functional analysis of variants of unknown clinical significance (VUS) in cultures of urine-derived RPC (u-RPC) of patients in a personalised manner[3,4]. This strategy: 1. Doubles the diagnostic rate for patients with SRNS; 2. Avoids unnecessary and potentially harmful treatments; 3. Reduces costs; 4. Addresses ethical and legal issues connected to extended genetic testing[2]; 5. Optimizes allocation of organ transplantation, minimising the risk of graft loss. We further implemented the personalised approach using innovative techniques such as 3D interface of the human glomerular capillary wall and a STED super-resolution microscopy analysis of the finest structure of the slit diaphragm to identify non-genetic patients with NS related to immunologic or permeability factor. In addition, we use scRNAseq analysis performed on RPC as well as on RPC-derived podocytes for biomarker identification. Finally, a retrospective model-based cost-efficiency analysis showed that personalised diagnosis in patients with SRNS diagnosed by WES analysis saved approximately 11.000€ (ranging from 600 to 21.138€) per patient taking into account only spared drug treatments and cost of WES analysis.

4. *Briefly summarize the work plan including the objectives, the rationale and the methodology, highlighting the novelty, originality and feasibility of the project;*

Objective 1: Implementation of a diagnostic algorithm for personalised management of NS

The project will enrol patients with age <40 years, with focal segmental glomerulosclerosis or minimal change lesion patterns at kidney biopsy and with resistance to a course of steroid treatment for WES screening (n=120). Selected patients will undergo genetic testing by WES followed by bioinformatic filtering to prioritize the identified variants as potentially pathogenic, VUS, or benign based on published algorithm[2]**.** A multi-disciplinary team from the coordinator's and partner's centres will define the pathogenic role of each variant by correlating it with the clinical phenotype (reverse phenotyping) of each patient[2,5]**.** To determine the pathogenicity of VUS, podocytes derived from patient u-RPC will be used. Readouts will be cytoskeleton integrity and podocyte detachment[3]. Furtherly, 3D organ-on-a-chip will be applied for live-cell confocal microscopy and 3D imaging for in-depth analysis of cell morphology, protein localization and functional processes. This diagnostic algorithm is already established in the coordinator's hospital and in the Tuscany region.

Objective 2: Personalised assessment of non-genetic forms and of relapse after transplant

Patients negative to genetic testing, including those with disease relapse after transplant, will be enrolled to detect circulating serum immunological or permeability factors. Serum patients will be investigated for the presence of circulating anti-nephrin antibodies by using an indirect enzyme-linked immunosorbent assay (ELISA). Nephrin antibodies as a possible cause of NS have been described in the lab of the external collaborator Astrid Weins, Harvard Medical School (see attached collaborative letter) and will be added to our algorithm for personalised diagnosis of NS. Once positive patients have been identified, their kidney biopsies will be analysed for the presence of anti-nephrin antibodies by applying high-resolution images with a confocal microscope. The

combination of optimized confocal parameters and the deconvolution with the Huygens software ensure sufficient resolving power for optimally imaging foot processes of the slit diaphragm. Incubation of biopsies with an anti-human IgG and anti-human nephrin, will allow to detect a specific co-localization of a punctate staining for IgG with nephrin, representing autoantibodies targeting nephrin. To confirm this, STED super-resolution microscopy analysis followed by immunostaining for the slit protein nephrin will be applied on cleared healthy human kidneys to reveal the slit diaphragm[7]. The slides will be incubated with patient serum to detect autoantibodies against nephrin in the serum. 3D organ-on-a-chip will be incubated with patient serum to detect circulating permeability factors that alter slit diaphragm permeability. Assay for albumin leakage (measured as FITC-albumin) will be performed. Live-cell confocal microscopy and 3D image analysis will be applied to analyse the functional processes.

Objective 3. Mapping potential biomarkers to predict patient outcome State of the art research techniques such as scRNAseq analysis[6] on u-RPC-derived podocytes cultures set up in the lab of the coordinator will be used to identify new biomarkers for patient stratification. This analysis will be performed from patients carrying variants in collagen genes, in podocyte genes, in other genes and in patients with a negative genetic testing. In order to validate biomarkers identified by scRNAseq for prognosis and disease outcome, we will perform qualitative/quantitative analysis for these biomarkers in urine samples and in kidney biopsies of patients. Statistical analysis and a correlation analysis between these biomarkers and clinical and laboratory information will be applied at the time of biopsy and at the last follow-up. This objective has the potential to identify novel biomarkers to further favour a personalised approach of NS in clinical practice.

Objective 4. Cost-effectiveness, ethical, and legal consequences of the proposed algorithm The project will apply a model-based cost-utility analysis to assess prospectively the economic implications of performing this diagnostic algorithm. The analysis will consider direct and indirect medical costs, and possibly direct non-medical costs and will include cost variations in the subsequent clinical surveillance and treatment. The same data will be also evaluated for genetic testing in proband's relatives. The outcomes will be measured as clinical effectiveness measures, quality-adjusted life-years (QALYs), using validated questionnaires. Results will be analysed in terms of incremental costs, consequences and, cost-effectiveness ratio (ICERc). Patient outcome (rate of progression toward kidney failure or increase of chronic kidney disease severity) and quality of life, tested by specific questionnaire, will be evaluated as clinical consequences. In order to ensure that the highest ethical, social and legal standards are met, specific questionnaire will be given to each patient and his/her family member and to each physician involved in the diagnostic procedure. Questionnaires will deal with communicating test results, Duty to disclose, Genetic discrimination, Informed consent, Privacy, Psychosocial impact, Reproductive issues, Societal values, Test utility. This objective will determine the cost-effectiveness of this diagnostic algorithm and the advantages of its application in comparison to current approaches in clinical practice.

5. *Describe the unmet medical and patient need that is addressed by the proposed work and the potential health impact that the results of your proposed work will have.*

The management of young patients with NS varies considerably across Europe with a limited access of European patients to benefit from the possibilities of a multidimensional diagnostic work-up leading to a cost-saving personalised care minimizing unnecessary treatment-related morbidity and maximizing renal outcomes before and after kidney transplantation. Spreading the access to this approach would save costs and time for all patients affected by NS with a more rational allocation of resources dedicated to healthcare and research[12]. Our retrospective model-based cost-efficiency analysis suggests a mean cost save. Prospective exploration of ethical, legal, and social aspects of this personalised approach will help further improving the diagnostic algorithm to incorporate patient-related aspects.

3.2. PRELIMINARY RESULTS (MAX. 2 PAGES)

Please include preliminary data obtained by the consortium members related to the proposed research work.

The coordinator and partner1 developed in collaboration an integrated diagnostic algorithm that permits a successful personalised genetic diagnosis in up to 60% of children and young adults with SRNS[2,5]. The algorithm is based on: 1. Selection of patients for genetic testing based on a series of clinical parameters that make the genetic cause highly likely; 2. WES analysis followed by an *in silico* analysis of an extended panel of genes associated with podocytopathies and other genetic syndromes reported to occasionally present with isolated SRNS (that is, as phenocopies of podocytopathies); 3. Genotype-phenotype correlation and reverse phenotyping, when it is appropriate, of the patient and its family based on filtered genetic findings; 4. A method for functional analysis of VUS in cultures of RPC obtained from the urine of patients in a personalised manner[3,4]. Our single-centre results demonstrate that this strategy 1. Doubles the diagnostic rate reported until now in the literature for patients with SRNS; 2. Avoids unnecessary and potentially harmful treatments, reduces costs, and addresses ethical and legal issues connected to extended genetic testing[2]; 3. Optimizes allocation of organ transplantation, minimising the risk of graft loss.

To achieve a better physiological resemblance *in vitro* of *in vivo* kidney functions, research is now moving from 2D cell cultures to 3D organ modelling. Thereby, the development of human organs-on-chips technology permits to create *in vitro* models that reconstitute complex 3D organ-level structures and to integrate crucial dynamic mechanical cues and chemical signals. Preliminary results showed that u-RPC can be specifically obtained from patients in a personalised manner maintaining their genetic and epigenetic background and they can reconstitute the human glomerular capillary wall on a three-lane organ-on-a-chip (Organoplate) by seeding primary endothelial cells and u-RPC-derived podocytes (Figure 1). Functional assays on organ-on-a-chip with u-RPC are important to establish the functional relevance of VUS in the onset of NS, especially in those cases in which traditional disease-causing genes are not involved or in those with complex genotypes. New technologies such as live-cell confocal microscopy and 3D imaging will be applied to analyse cell morphology, cytoskeleton architecture and functional abnormalities. This activity will thereby increase the diagnostic rate, improve the prediction of prognosis and will finally help in guiding the clinical management of patients, stratifying them according to genetic findings. Based on these evidences, we propose a coordinated strategy to implement this algorithm extending the personalised diagnosis also to non-genetic patients using innovative techniques also for diagnosis of immunologic forms. Strikingly, we extended the personalised approach to non-genetic patients with frequent relapses or with disease relapse after kidney transplant. Preliminary results showed that this approach enabled to increase the rate of relapse prediction after transplant from the current 30%[13] to 83.3% (Figure 1).

To identify circulating immunologic factors as causes of frequent relapses in non-genetic patients with frequent relapses or with disease relapse after kidney transplant we employed sophisticated technologies such as high-resolution images with a confocal microscope and STED super-resolution microscopy. Incubation of kidney biopsies with an anti-human IgG and anti-human nephrin allowed to detect a specific co-localization of a punctate staining for IgG with nephrin, representing autoantibodies targeting nephrin in the glomerular filtration barrier. The combination of optimized confocal parameters (smaller pinhole diameter of 0.3 Airy Unit and hybrid detectors with the highest photon collection efficiency and lowest dark signal) and the deconvolution with the Huygens software ensure sufficient resolving power for optimally imaging foot processes, the slit diaphragm, allowing to identify anti-nephrin antibody deposition (Figure 1). Moreover, preliminary results showed a STED super-resolution microscopy analysis of the finest structure of the slit diaphragm. We cleared healthy human kidneys using a hydrogel-based protocol[7], and stain for nephrin to reveal the slit diaphragm (Figure 1). STED super-resolution microscopy analysis will also be helpful to identify anti-nephrin antibodies in the serum of patients with frequent relapses. In addition, the 3D interface of the human glomerular capillary wall will be used to detect circulating

permeability factors in the serum of non-genetic patients with frequent relapses or with disease relapse after kidney transplant. Alteration of slit diaphragm permeability has been evaluated as albumin leakage, measured as FITC-albumin, in the filtrate collected from the bottom chamber (Figure 1). Moreover, the coordinator and partner1 developed the transcriptomic profile of RPC as well as of RPC-derived podocytes by scRNAseq analysis for biomarker identification (Figure 1). In addition, the coordinator performed a retrospective cost analysis using previous data from patients with SRNS diagnosed by WES analysis from 2019 to 2021, taking advantage from the collaboration with Dr. S. Bellelli of Istituto di Ricerche Economico Sociali (IRES), Turin, Italy. The analysis took into account direct medical cost, focusing in particular to drugs prescribed to patients before the use of genetic testing in the diagnostic algorithm. According to this, the analysis aimed to include possible cost variations in the subsequent clinical surveillance and treatment for the disease management. The outcomes of the intervention were measured as clinical effectiveness measures. Results were expressed in terms of incremental costs and incremental consequences and, when appropriate, incremental ICERc. The outcome analysis was conducted with the Regional Health System perspective and all data expressed in Euros; the costs were referred to Regional Healthcare Reimbursement and Pricing System. Thus, the analysis addressed for the first time the economic impact of the in-clinic use of WES in patients affected by podocytopathies, quantifying part of the gains in terms of healthcare and economic impact beyond the genetic diagnosis. This preliminary analysis, considering a subgroup of 20 patients and performed taking into account potentially spared drug treatments by using WES analysis and the cost of WES analysis itself, showed that personalised genetic diagnosis by WES gives a mean cost save of approximately 11.000€ (ranging from 600 to 21.138€), per patient. This value has been calculated by micro-costing analysis using the costs for each drug (the costs are referred to the Regional Healthcare Reimbursement al Pricing System), calculated taking into account the dose per day, multiplied for the time of the prescription for each considered patient. This amount resulted higher compared to the cost of WES sequencing per patient that is actually 3.600€ at coordinator centre. The cost difference could probably increase accounting also other medical direct and indirect expenses.

3.3. CHANGES IN THE PROPOSAL BETWEEN THE PRE- AND FULL-PROPOSALS (MAX. 1 PAGE)

*Please include the main changes, i.e. inclusion and role of a new partner (an additional partner is **only** allowed from the following underrepresented funding organisations:* **ANID (Chile), MSR (Croatia), SMWK (Saxony); VIAA (Latvia) and TUBITAK (Turkey)**

The maximum number of partners can be expanded to 7 if an additional partner from these underrepresented funding organisations is included), how the recommendations from the pre-proposal evaluation have been addressed, budget amendments and shifting of activities (if any).

No changes are performed.

3.4. WORK PLAN INCLUDING REFERENCES (MAX. 8 PAGES)

Please include: aims, methodology, role of each participant, timeline, work packages, project coordination and management, innovation, risk assessment, added value of the proposed solutions to address a medical need compared to existing ones. Please include a list of abbreviations.

NS in children and young adults is a frequent medical problem of very diverse pathophysiology and prognosis[1]. Current diagnostic algorithms fail to avoid under- and overtreatment of patients with toxic drugs as defining the underlying cause is frequently difficult. We have developed a diagnostic algorithm of stratifying patients through advanced genetic testing, reverse phenotyping, and personalised disease models. This can double the current diagnostic rate in patients not responding to first line therapy and to predict disease relapse in those that progress to end stage kidney disease and have to undergo kidney transplant.

The aims of this project are:

1. implementation of this diagnostic algorithm in selected European sites by a) selecting patients for a personalised genetic diagnosis, b) WES and bioinformatic prioritization of potentially pathogenic variants, c) validating genotype-phenotype correlation for a personalised diagnosis, and d) personalising the assessment of VUS by functional studies with patient u-RPC and 3D organ-on-a-chip disease models.

2. Personalising the assessment of non-genetic forms and of relapse after transplant by a) identifying patients with steroid-dependent NS or frequent relapses, b) assessing patients with proteinuria relapse after kidney transplant, c) personalising the detection of immunologic factors by using STED super-resolution microscopy and d) personalising the detection of circulatory permeability factors by using a 3D organ-on-a-chip model system.

3. Assessing the cost-effectiveness as well as clinical, ethical, and legal consequences of the proposed algorithm by a) a multicentre model-based cost-utility analysis of the proposed algorithm and by assessing the b) clinical, c) ethical, and d) legal consequences in close conjunction with the study participants and the respective patient organisations by standardised questionnaire tools.

To achieve these aims, the coordinator, Prof. Romagnani will take advantage of the collaboration with the partners Prof. Lazzeri (partner1), Prof. Cruzado (partner2) and Prof. Anders (partner3). This collaboration could create a strong scientific team ideal to face the challenges proposed in the project. In addition to the scientific excellence of each partner (see publication track) and the weight that the individual participants carry in the project, two features clearly emerge: a diverse and synergistic array of scientific and technological expertise, which represent a real and full complementariness of these expertises. This is optimally suited for the successful achievement of the workpackages assigned to each partner. The coordinator (clinical nephrologist and leading kidney researcher) established the diagnostic algorithm for personalised management of NS by performing WES, bioinformatic prioritization of variants followed by genotype-phenotype correlation for personalised diagnosis[2]. The coordinator and partner1 set-up a patented method for preparation of RPC cultures from the urine of patients to support personalised diagnosis (patent number: FI2013A000303)[3]. Meyer Children's Hospital is a highly specialized pediatric hospital (third level hospital) and a national referral centre for high pediatric complexity. It is part of the National Health Service and in particular of the Health System of the Tuscany Region. It is integrated with the University of Florence with which it carries out, in a unified manner, assistance, teaching and research functions. The institute ensures the management, support, promotion and enhancement of clinical research thanks to the expertise of the appointed offices (Strategic Partnership and Innovation Office, Research Promotion and Enhancement Office, Technology Transfer Support Office, Data analytics and IT Centre, Clinical Trial Office), increasing the feasibility of the project. Partner1 showed the expertise and the know-how in developing the human glomerular capillary wall on a three-lane organ-on-a-chip, the STED super-resolution microscopy analysis and scRNAseq with 10x Genomics Chromium system. Indeed, the coordinator and partner1 developed the

transcriptomic profile of RPC as well as of RPC-derived podocytes by scRNAseq analysis for biomarker identification. These technologies are already available in the Laboratory of Nephrology and a dedicated staff is highly trained with all instruments. The Department of Biomedical, Experimental and Clinical Sciences of the University of Florence, where the laboratory of Nephrology is located and the research of partner1 will be carried out, has been selected by the Italian Minister of University and Research (MIUR) as a Department of Excellence in 2018. The laboratory is equipped with all instruments proposed in the project to complete all workpackages. In addition, the Department has dedicated staff who can provide support for the analysis of bioinformatics data. The laboratory works in close continuity with the Clinical Unit of Nephrology of the Meyer Children's Hospital and with the Unit of Nephrology of the Azienda Ospedialiera Universitaria Careggi of Florence, increasing the feasibility of the project and the possibility to bring basic science discoveries to translational applications to patients. Partner2 is a leading expert in clinical transplantation directing the Nephrology Department at the Bellvitge University Hospital in Barcelona that is also the leading centre for kidney transplantation in Spain performing >200 kidney transplant per year. Partner3 is a leading scientist and expert in clinical nephrology. The LMU university hospital is the second largest University hospital in Germany, providing care for large numbers of children and adults with NS and able to implement the diagnostic algorithm as proposed. These partners will collect peripheral blood samples from selected patients and their families referred to their centres in order to assess WES by coordinator. After the selection of variants identified by WES, the coordinator and all partners will jointly analyse the correlation of genetic findings with the clinical phenotype of each patient and the diverse, balanced and synergistic partner's expertise will permit to address a personalized diagnosis. Moreover, partners2 and 3 have already been trained by partner1 to isolate RPC from the urine of patients (see publications).

The work plan for this project is schematically outlined in the Gantt chart showing in detail the WPs.

WP1: Implementation of an integrated diagnostic algorithm for personalised management of NS

Task1: Selection of patients for personalised genetic diagnosis (Timing: 0-12 months).

The project will enrol patients with age <40 years, with focal segmental glomerulosclerosis or minimal change lesion patterns at kidney biopsy and with resistance to a course of steroid treatment referred to the coordinator and partner centres (2 and 3) for WES screening. In this cohort of patients, we will also include patients with or without relapse after renal transplant. We will expect to enrol 120 patients referred to all centres. Clinical and laboratory exams, ultrasound scanning, familial and clinical history, information about therapy (ongoing and previous treatments), will be collected in order to generate a common database for selected patients. Moreover, coordinator and partner centres (2 and 3) will collect DNA samples (peripheral blood samples) from selected patients and their families. Other affected relatives could be eventually enrolled based on the familial history of the disease. The database for detailed analysis of patients will be shared among partners and with the ERKNet, the European Kidney Disease Reference Network (https://www.erknet.org), of which the coordinator is member, by respecting data security.

Task2: Whole Exome Sequencing and bioinformatic prioritization of variants (Timing: 4-32 months).

Selected patients will undergo genetic testing by WES followed by bioinformatic filtering for extended panel of genes associated with podocytopathies and other genetic syndromes reported to occasionally present with isolated SRNS. The identified variants will be classified as potentially pathogenic variants, VUS, or benign variants, in agreement with the interpretation guidelines of the American College of Medical Genetics and Genomics (ACMG)[4], and based on published

algorithm[2]. Partners will retain only potentially pathogenic variants and VUS. After the interpretation, the candidate variant(s) will be validated by Sanger sequencing. Copy number variation will also be analysed in samples run.

Task3: Genotype-phenotype correlation for personalised diagnosis (Timing: 5-36 months).

After the selection of variants, a multi-disciplinary team including specialists from coordinator and all partner centres will jointly analyse the correlation of genetic findings with the clinical phenotype of each patient. Indeed, the definition of the pathogenic role of each variant will be established with the joint efforts of geneticists, nephrologists and basic researchers in order to integrate the clinical and genetic information. This analysis will cluster patients in 3 groups based on variants: 1. variants fitting bioinformatic prioritization criteria and the phenotype and already reported in the literature will be defined as pathogenic variants. Patients will then be addressed to genetic counselling at coordinator and each partner centres. 2. variants fitting bioinformatic prioritization criteria but not fitting the phenotype and not previously reported in the literature will be defined as potentially pathogenic variants. In these cases, the coordinator and partners will perform an accurate clinical re-evaluation of the patients, that will eventually include also reverse phenotyping (i.e. analysis of clinical phenotype directed by the results of genetic screening) of all the patients and their family. These will lead to a conclusive genetic diagnosis in a substantial proportion of cases, who will then be provided with genetic counselling. 3. variants fitting the phenotype but not fitting bioinformatic prioritization criteria will be defined as VUS. In these cases, partner1 will perform functional assessment of selected variants with u-RPC cultures of affected patients, in order to address the potential role of the variants in determining specific aspects of the clinical phenotype. Afterwards, patients will be addressed to dedicated clinical management.

Task4: Personalised assessment of VUS by functional studies with u-RPC and 3D organ-on-a-chip (Timing: 5-36 months).

To determine the pathogenicity of VUS and to understand its role in the onset of the disorder, partner1 will develop an adequate disease personalised modelling. To this aim, urine of patients with VUS will be collected and RPC isolated (from referred centre of each patient) with the standardized method set-up by the coordinator and partner1[3] (patent number: FI2013A000303). Partner2 and 3 will send RPC cultures to Partner1, who will develop the appropriate functional test (depending on the genetic variants) by using patient-specific podocytes cells derived after u-RPC differentiation *in vitro*. Readouts will be cytoskeleton integrity and podocyte detachment evaluated with Annexin-PI by FACS analysis[3]. For better physiological and pathological resemblance of *in vivo* kidney functions *in vitro*, partner1 will recreate the tissue-tissue interface of the human glomerular capillary wall on a three-lane chip Organoplates™ by seeding primary endothelial cells and u-RPC-derived podocytes[5]. A microperfusion pump will generate the cyclic mechanical forces and shear stresses due to glomerular blood and urine flow recreating the physical forces present in the local glomerular microenvironment. In these models, a combination of kidney-on-a-chip devices with forefront microscopy techniques, such as live-cell confocal microscopy, 3D image analysis, and STED super-resolution microscopy will be implemented. This creates an integrated platform useful for in-depth analysis of cell morphology (plasticity of foot processes, podocyte detachment, polarization, tight junction), protein localization (specific podocyte markers), and functional processes (cytoskeleton dynamics, filtration capacity). u-RPC obtained from patients negative to genetic test will be used for comparisons.

Risk assessment of WP1: WP1 will commence immediately as the diagnostic algorithm is already well established in the coordinator centre. Protocol for isolation of u-RPC is standardized. Urine samples will be collected from patients until a culture will be established. Moreover, coordinator and Partner1 have already demonstrated proficiency on developing adequate disease personalised modelling, 3D organ-on-a-chip and super-resolution microscopy analysis (see publications and preliminary results) depending on the genetic variants. All the equipment are available in the centre of partner1. Thus, no major setbacks are foreseen in this phase.

WP2: Personalised assessment of non-genetic forms and of relapse after transplant

Task1: Assessment of patients negative to the diagnostic algorithm (Timing: 9-36 months).

Patients negative to the genetic testing (performed in WP1) with frequent relapses, will be enrolled in order to investigate the presence of putative serum immunologic or circulating permeability factors. The coordinator and partners 2 and 3 will collect peripheral blood samples during either complete (urine protein to creatinine ratio, UPCR < 0.3 g/g), partial remission (>50% reduction) and active disease (UPCR > 3g/g). Based on the diagnostic rate of the algorithm[2], we predict to select for this analysis 48 patients (40% of patients enrolled in WP1).

Task2: Assessment of patients with proteinuria relapse after kidney transplant (Timing: 9-36 months).

Patients negative to the genetic testing but with disease relapse after kidney transplant will be selected to investigate the presence of immunologic or circulating permeability factors. The coordinator and partners 2 and 3 will collect peripheral blood samples from 20 patients before transplant, and before, and after plasma exchanges after transplant.

Task3: Personalised detection of immunologic factors by using STED-analysis (Timing: 9-36 months).

Serum patients enrolled in task1 and 2 will be investigated for the presence of circulating anti-nephrin antibodies by using an indirect ELISA. We will take advantage from the collaboration with Prof. Weins, who developed and standardized this method. Once positive patients have been identified, partner1 will analyse their kidney biopsies for the presence of anti-nephrin antibodies by applying high-resolution images with a confocal microscope. The combination of optimized confocal parameters and the deconvolution with the Huygens software ensure sufficient resolving power for optimally imaging foot processes of the slit diaphragm. Incubation of biopsies with an anti-human IgG and anti-human nephrin, will allow to detect a specific co-localization of a punctate staining for IgG with nephrin, representing autoantibodies targeting nephrin. To confirm this, partner1 will clear healthy human kidneys optically using a hydrogel-based protocol[6], followed by nephrin immunostaining and STED super-resolution microscopy analysis with a Leica SP8 STED 3X. The optical clearing and the high resolution achievable with STED super-resolution microscopy revealed the finest structure of the slit diaphragm and allowed localizing the spatial distribution of nephrin at the nanometer scale. The healthy human kidneys will be incubated with serum patients identified as positive for the presence of circulating anti-nephrin antibodies by ELISA. After incubation with an anti-human IgG, we will verify the presence of autoantibodies against nephrin in patient's serum looking for specific co-localization of IgG with nephrin.

Task4: Personalised detection of circulating permeability factors by using 3D organ-on-a-chip (Timing: 9-34 months).

Partner1 will recreate the tissue-tissue interface of the human glomerular capillary wall on a three-lane chip Organoplates™ by seeding primary endothelial cells and u-RPC-derived podocytes. The chip will be incubated with patient serum collected in task1 and 2 for 24 h, in order to evaluate the presence of circulating permeability factors that alter slit diaphragm permeability. The latter will be evaluated as albumin leakage (measured as FITC-albumin) in the filtrate collected. Live-cell confocal microscopy and 3D image analysis will permit in-depth analysis of functional processes. In addition, patner1 will correlate albumin leakage with proteinuria measured at the time of serum collection, by linear regression analysis.

Risk assessment of WP2: WP2 will commence immediately as partner1 has already shown evidence that investigation of anti-nephrin antibody deposition on renal biopsies is feasible by applying super-resolution imaging with a confocal microscope. Moreover, STED super-resolution microscopy and 3D organ-on-a-chip are already available in the laboratory. Protocol to reveal the finest structure of the slit diaphragm and allowed localizing the spatial distribution of nephrin at the nanometer scale in cleared healthy human kidneys has already been setting up (see preliminary results). Thus, no major setbacks are foreseen in this phase. Risks connected to this objective relate

mostly to the technical aspects of the serum patient investigation for the presence of circulating anti-nephrin antibodies by using an indirect ELISA. Partners will take advantage from the collaboration with Prof. Weins, who developed and standardized this method. Coordinators and partners are confident that their experience combined with the collaboration with Prof. Weins will enable the WP to overcome any technical obstacles. Further risks relate mostly to the technical aspects of STED super-resolution microscopy, however highly trained staff (Dr. ML. Angelotti) will provide technical support to mitigate these potential risks. Overall, these skills make this specific WP feasible which, therefore, will be completed on time.

WP3. Mapping potential biomarkers to predict patient outcome

Task1: Single cell RNA sequencing analysis of u-RPC for biomarker identification (Timing: 13-36 months).

The coordinator and partner1 will use scRNAseq in order to provide molecular insights among pathways potentially involved in the development of podocyte lesions and to enable the identification of potential biomarkers for patient stratification. They will select u-RPC-derived podocytes from 1. patients carrying variants in collagen genes (n=4, 2 females and 2 males); 2. patients carrying variants in podocyte genes (n=4, 2 females and 2 males); 3. patients carrying variants in other genes (n=4, 2 females and 2 males); 4. patients with a negative genetic testing (n=4, 2 females and 2 males). scRNAseq with 10X Genomics Chromium system, (10x Genomics) and a subsequent sequencing on Illumina NextSeq550 (Illumina Inc.) will be performed. A rigorous single cell bioinformatics pipeline, (10x Genomics Cell Ranger pipeline, version 3.0.1), will be used to analyse the data[5]. This includes quality control and normalization procedure and unsupervised clustering to identify cell subpopulations and robust differential marker genes (Uniform Manifold Approximation and Projection (UMAP) algorithm). It will be possible to identify the signatures of patient specific u-RPC of the four groups arising novel patterns of podocytopathies with strong impact on prognosis and disease outcome.

Task2: Validation of potential biomarkers to predict patient outcome (Timing: 13-36 months).

Partner1 will perform qualitative/quantitative analysis for markers identified by scRNAseq in urine samples and in kidney biopsies of patients. To validate potential biomarkers for prognosis and disease outcome, the coordinator and partner1 will perform a statistical analysis and a correlation analysis between the biomarkers identified by scRNAseq and clinical and laboratory information collected at time of biopsy and at the last follow-up.

Risk assessment of WP3: partner1 in collaboration with coordinator have already shown evidence that scRNAseq technology is already available. Protocol to perform scRNAseq analysis on RPC and on u-RPC-derived podocytes has already been setting up (see preliminary results). scRNAseq with 10X Genomics Chromium system and a subsequent sequencing on Illumina NextSeq550 will be performed. A rigorous single cell bioinformatics pipeline, (10x Genomics Cell Ranger pipeline, version 3.0.1), will be used to analyse the data. Bioinformaticians from the onsite Genetics facility will provide support for data analysis. Risks connected to this WP relate mostly to the technical aspects of the sample preparation for single cell analysis on the10x Genomics instrument, however highly trained staff (Dr. B. Mazzinghi) who is on site at the Meyer Children's Hospital will provide additional technical support to mitigate this potential risks. Overall, these skills make this specific WP feasible which, therefore, will be completed on time.

WP4. Cost-effectiveness, clinical, ethical, and legal consequences of the proposed algorithm

Task1: Multicentre model-based cost-utility analysis of personalised genetic diagnosis (Timing: 6-36 months).

The coordinator and partner2 will perform a cost-utility analysis to prospectively assess the economic implications of performing a genetic testing by WES in 120 patients affected by NS, taking advantage from the collaboration with Dr. S. Bellelli of IRES, Turin, Italy. The comparator will be the standard diagnostic pathway including, among other exams, in particular the renal biopsy and the genetic testing by gene panel. The analysis will take into account: a. direct medical costs (e.g. laboratory tests, medical and nursing services, drugs, medical supplies, diagnostic imaging,

hospitalization and food services), b. possibly direct non-medical costs (e.g. expenditures as the result of an illness but are not involved in the direct purchasing of medical services, such as costs of transport, diet, paid domestic support and informal care, collected by questionnaires), and c. other indirect costs of patients and caregivers (eg. expenses incurred from the productivity losses as a result of the morbidity associated with the disease). When possible, these data will be also collected for the economic evaluation of cascade genetic testing in proband's relatives. The outcomes of the intervention will be measured as clinical outcomes measures (e.g. number of diagnosis, diagnosis reclassification, treatment changes, number of spared procedures), QALYs, using validated questionnaires. Data will be collected by healthcare administrative databases and by electronic Case Report Form (eCRF) for gathering information aimed to estimated direct non-medical and indirect costs of patients and caregivers. Results will be expressed in terms of incremental costs and incremental consequences and, when appropriate, ICERc. The analysis will be conducted with the three partners' National Health Systems perspectives (Italy, Spain and Germany) and all data will be expressed in Euros. Thus, this analysis will address for the first time the comprehensive economic impact of the in-clinic uses of WES in patients affected by NS; in fact, such analysis potentially could quantify all the gains in terms of healthcare and economic impact beyond the genetic diagnosis.

Task2: Clinical consequences of the proposed diagnostic algorithm (Timing: 6-36 months).

In order to address the clinical consequences of the application of the algorithm, the coordinator and partner2 will evaluate patient outcome (rate of progression toward end-stage kidney disease or increase of chronic kidney disease severity) and quality of life. For quality of life, they plan to administer a specific questionnaire to 1. Each patient and his/her family member; 2. Each physician involved in the diagnostic procedure. Questionnaires will be given at referral, diagnosis and at regular intervals of 4 months and will deal with the following aspects: global health, anxiety, fatigue domains; mobility, school and work; social interactions; sleep-related impairment. The questionnaires will be administered by trained staff. When available, questionnaires already validated for specific domains (e.g., psychosocial burden, reproductive issues, etc) will be used; for the others, the questionnaires will be set up by semi-structured interview or focus group discussions including clinicians and patients.

Task3: Ethical, social and legal consequences of the proposed diagnostic algorithm (Timing: 6-36 months).

In order to ensure that the highest ethical, social and legal standards are met, we plan to administer a specific questionnaire to 1. each patient and his/her family member; 2. each physician involved in the diagnostic procedure. When available, questionnaires already validated for specific domains (e.g., psychosocial burden, reproductive issues, etc) will be used; for the others, the questionnaires will be set up by semi-structured interview or focus group discussions including clinicians and patients. The questionnaires will be administered by trained staff.

Questionnaires will deal with the following aspects:

Communicating Test Results Questionnaires will check if: 1. genetic test results were discussed with patients in an understandable and compassionate manner; 2. if patients understood the information actually provided from the genetic test; 3. If results were communicated in person.
Duty to Disclose Questionnaires will check if: 1. the results of the test had implications for patient's family members; 2. if the patient was encouraged to discuss results with other family members.
Genetic Discrimination Questionnaires will check if the potential for discrimination impacted an individual's decision to utilize genetic testing and if any individual was discriminated in employment, health insurance or social groups as a consequence of genetic testing.
Informed Consent Questionnaires will evaluate if informed consent addressed efficiently: 1. Risks, limitations, and benefits of testing or not testing; 2. Alternatives to genetic testing; 3. Details of the testing process; 4. Privacy/confidentiality of test results; 5. The voluntary nature of testing; 6. Potential consequences related to results, including impact on health, emotional and psychological reactions, treatment/prevention options and ramifications for the family.

Privacy Questionnaires will evaluate if the privacy was respected and in particular, who should have or needs access to that information.
Psychosocial Impact Questionnaires will check if referrals to genetic counsellors, psychologists, or social workers were appropriately be made as needed.
Reproductive Issues Questionnaires will check if informed reproductive decisions and medical care and parents were carefully considered and discussed with a physician or geneticist counsellor.
Societal Values Questionnaires will check if personal factors, family values, and community and cultural beliefs influenced responses to genetic information and testing or if results of genetic tests influenced one individual to change his or her lifestyle or behaviour.
Test Utility for some genetic forms of NS, the utility of genetic test results may be limited by lack of treatments but still be beneficial from avoiding side effects of unnecessary treatments. Questionnaires will check if these issues were discussed with patients.

To set up and evaluate the questionnaires coordinator will be supported by the Ethical Committee (reference person: Dr. M. Falconi, https://www.meyer.it/index.php/ricerca-e-innovazione/comitato-etico) and by the Clinical Trial Office (Reference person: Dr. A. Pugi, https://www.meyer.it/index.php/ricerca-e-innovazione/clinical-trial-office) of Meyer Children's Hospital. The ethical committee located at the Meyer Children's Hospital that includes ethical experts, geneticists, law and social science experts, epidemiologists, biostatisticians, representatives of patient associations is an independent body, without hierarchical subordination constraints towards other authorities. The main objective is to guarantee the protection of the rights, safety and well-being of the patients involved in a research, providing a public guarantee of protection. This aim is achieved through the evaluation of all clinical protocols according to the international standards of good clinical practice (GCP ICH6) and the ethical principles established in the Declaration of Helsinki. The Clinical Trial Office is a body that operates independently from the Pediatric Ethics Committee, but jointly with this to ensure the protection of the welfare, safety and rights of all those involved in the research. The Clinical Trial Office will provide scientific, administrative, epidemiological, biostatistics, clinical and infrastructural services to coordinator and will also be involved in reanalysis of questionnaires submitted to patients recruited by partner2 and 3. All the questionnaires will be administered by the nephrologist with genetic expertise together with a psychologist.

Risk assessment of WP4: All the knowhow needed to perform cost-utility analysis and set-up the proposed questionnaires is available at the center of the coordinator. Further to this, an external collaborator expert in Health Economics and calculations of cost-effectiveness of diagnostic procedures (see attached collaborative letter) will support the analyses further minimizing the risks.

References:

1. Kopp JB*, Anders HJ*, et al. Podocytopathies. Nat Rev Dis Primers. 2020; 6:68.

2. Landini S, et al. Reverse Phenotyping after Whole-Exome Sequencing in Steroid-Resistant Nephrotic Syndrome. Clin J Am Soc Nephrol. 2020; 15:89-100.

3. Lazzeri E, et al. Human Urine-Derived Renal Progenitors for Personalized Modeling of Genetic Kidney Disorders. J Am Soc Nephrol. 2015; 26:1961-1974.

4. Richards S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med.2015,17:405-424.

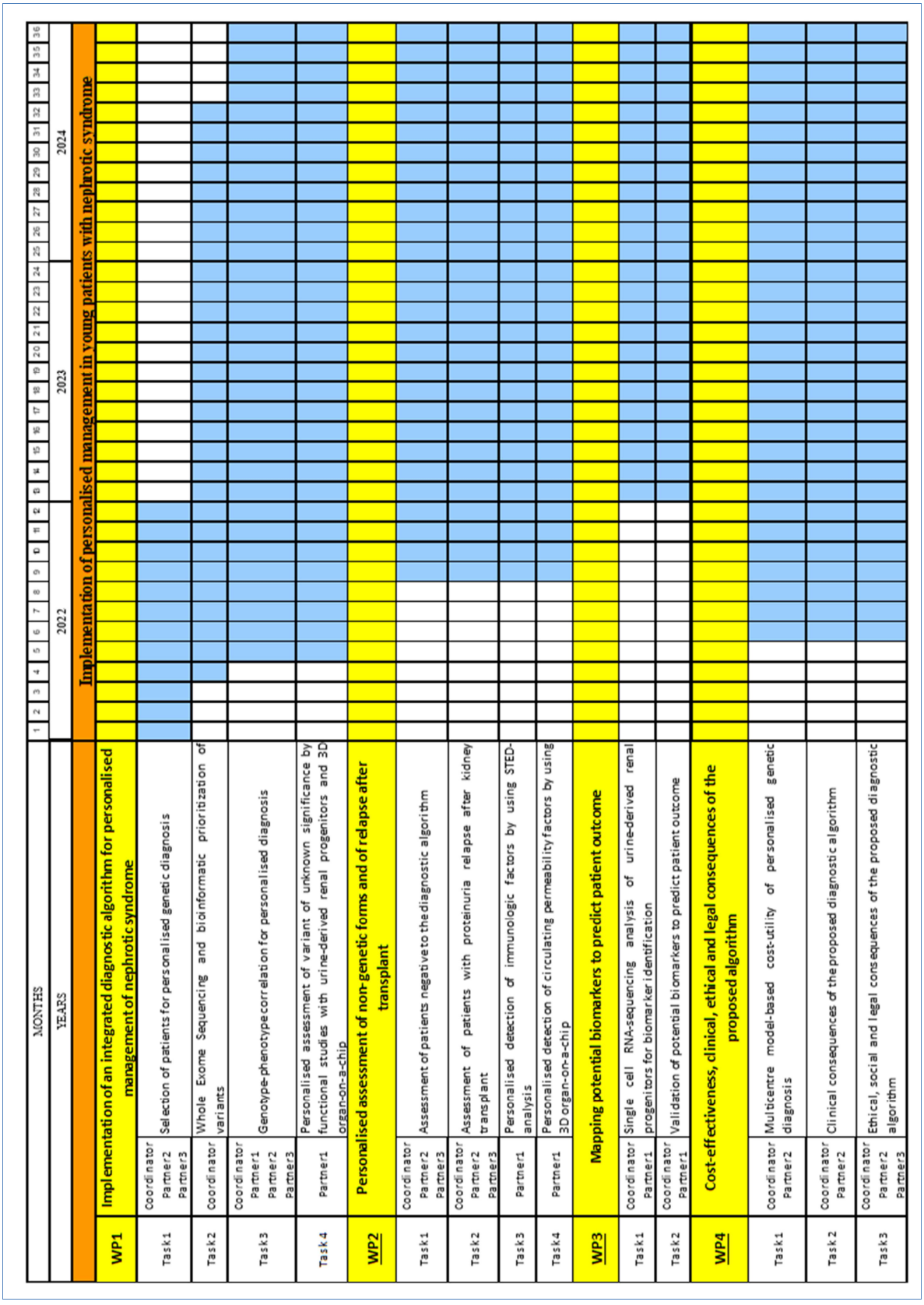
5. Peired AJ, et al. Acute kidney injury promotes development of papillary renal cell adenoma and carcinoma from renal progenitor cells. Science Translational Medicine. 2020; 12:eaaw6003.

6. Motrapu M, et al. Drug Testing for Residual Progression of Diabetic Kidney Disease in Mice Beyond Therapy with Metformin, Ramipril, and Empagliflozin. J Am Soc Nephrol. 2020; 31:1729-1745.

List of abbreviations:

NS: nephrotic syndrome
WES: whole exome sequencing
RPC: renal progenitors
scRNAseq: single cell RNA sequencing
SRNS: steroid resistant nephrotic syndrome
VUS: variants of unknown significance
u-RPC: urine-derived renal progenitors
ELISA: enzyme-linked immunosorbent assay
QALYs: life-years adjusted for quality of life
ICERc: cost-effectiveness ratio
IRES: Istituto di Ricerche Economico Sociali
MIUR: Italian Minister of University and Research
ACMG: American College of Medical Genetics and Genomics
UPCR: urine protein to creatinine ratio
UMAP: Uniform Manifold Approximation and Projection
eCRF: electronic Case Report Form
GCP: good clinical practice

3.5. DIAGRAM WHICH COMPILES THE WORK PLAN, TIMELINE, SEQUENCING OF WORK PACKAGES, CONTRIBUTION OF THE PARTNERS TO EACH WORK PACKAGE AND THEIR INTERACTIONS (TIMEPLAN, GANTT AND/OR PERT, MAX. 1 PAGE)



3.6. JUSTIFICATION OF REQUESTED BUDGET AND TOTAL PROJECT COSTS (MAX. 1 PAGE)

Please justify the resources to be committed. Where applicable, also specify co-funding from other sources necessary for the project.

Coordinator:

Personnel: OWN FUNDING: 1 Full professor and 1 Staff Physician for clinical data collection and analysis, 1 Staff Biologist for genetic data analysis (18 total months for € 96.312,5).

ON FUNDING: 2 fixed-term contracts for whole exome and scRNA sequencing (36 total months, € 75.000,0).

Consumables: Kits for whole exome sequencing and scRNA sequencing

Other: Two open access publications

Partner 1:

Personnel: OWN FUNDING: 2 Associate Professors for data analysis, 1 Technician for confocal microscopy and a STED-super resolution microscopy (20 total months, € 97.190,0).

ON FUNDING: 1 fellowship for renal progenitor isolation, 3D organ-on-a-chip assay and scRNA library preparation (24 months, €25.000/year), 1 fellowship for bioinformatic analysis (12 months, €25.000/year).

Consumables: Cell culture material, 3D organ-on-a-chip, reagents for confocal and STED microscopy, kits for scRNA library preparation.

Other: One open access publication.

Partner 2:

Personnel: One postDoc researcher full-time dedication for three years (36 Person-Months) that will be in charge of the collection and process of cell cultures, and to perform and export project data is required. Two clinical investigators with part time dedication (10 and 5 Person-Month) will be in charge of the obtention of informed consent and clinical and analytical data collection, as well as further data evaluation (their costs are not required).

Consumables: Cell culture material: media (EGM-MV), FBS, antibiotics, reagents, antibodies for FACs CANTO (partially covered by previous grants). Kits for whole exome sequencing.

Travel: Travel for consortium meetings and presentations of results in Congresses.

Other: Sample shipment. Publication costs (covered by previous grants).

Subcontracting: Financial audit certificate.

Partner 3:

Personnel: One lab technician (27 PM) urine sampling and processing, cell culture and assays, data analysis and exportation

One clinician (12 PM) for informed consent, clinical data collection covered by institution.

Consumables: Cell culture material: media (EGM-MV), FBS, antibiotics, reagents, biochemical, antibodies for FACS CANTO in order to execute tasks, bioassays, plastic and glass ware. Kits for whole exome sequencing.

Travel: Travel for consortium meetings and presentations of results in Congresses.

Other: User fees for centralized FACS sorting service and bioimaging unit.

Sample shipment costs, publication fees.

3.7. ADDED VALUE OF THE PROPOSED INTERNATIONAL COLLABORATION (MAX. 1 PAGE)

Please describe the added value of the transnational collaboration; sharing of resources (registries, diagnosis, biobanks, models, databases, diagnostic and informatics tools, etc.), platforms/infrastructures, harmonisation of data and sharing of specific know-how.

The management of young patients with NS varies considerably across Europe with a limited access of European patients to benefit from the possibilities of a multidimensional diagnostic work-up leading to a cost-saving personalised care minimizing unnecessary treatment-related morbidity and maximizing renal outcomes before and after kidney transplantation. Given that public health system of the Tuscany region has already taken advantage from the successful application in the coordinator hospital of a diagnostic algorithm for personalised management of NS, the proposal aims at spreading this diagnostic algorithm to German and Spanish partner centres. The involvement of LMU and Bellvitge Hospital, that represent leading centres in the field in Germany and Spain, will optimize the implementation strategy across Europe. Thus, the proposal based on the transnational collaboration between the coordinator (Prof. Romagnani) and their partners Prof. Lazzeri, Prof. Cruzado, and Prof. Anders. This collaboration creates a strong scientific team ideal to face the challenges proposed in the project. Indeed, a diverse, balanced and synergistic array of scientific excellence of each partner and technological expertise (see publication track) is optimally suited for the successful achievement of the WP assigned to each partner, and a real and full complementariness of these expertise will collectively permit to address all the aims of the proposal. Moreover, the already established collaboration between the coordinator and the participating partners is demonstrated in several publications, where partners2 and 3 use the isolation method of u-RPC to make diagnosis or to predict patient prognosis[4,14]. In addition, the coordinator belongs from 2016 to the ERKNet consortium, where expert nephrology centres provide healthcare to more than 40.000 patients with rare and complex kidney disorders. The objective of ERKNet is pursued by the determination and sharing of uniform accepted diagnostic criteria, healthcare management, patient prognosis and research strategies. This project moves in the same direction and aims at applying the diagnostic algorithm of coordinator to the daily practice of partner2 and 3 centres, implementing personalised diagnostic strategy. Therefore, the proposal aims to share additional resources among participating partners, such as registries, diagnosis, databases by respecting data security, platforms/equipments for WES, STED super-resolution microscopy analysis, 3D kidney-on-a-chip models and scRNAseq analysis. The participating partners will organize routine web meetings, which will allow the updating of the participating partners to the progression of project workplan. Patient organizations on NS will be constantly involved. Thus, this network represents an expansion of a previously consolidated collaboration, creating a strong scientific team ideal for the challenge of designing a better-personalised healthcare in nephrology.

3.8. POTENTIAL IMPACT AND EXPLOITATION OF EXPECTED PROJECT RESULTS (MAX. 1 PAGE)

Please indicate how the proposed study could influence or change the way that health care is delivered and the effect of the expected results on future clinical, public health and/or other socio-economic health-relevant applications (if applicable also for commercial exploitation), if available.

The heterogeneity of genetic and non-genetic causes among patients with SRNS with different prognosis and response to treatments urgently requires a personalised approach. The diagnostic algorithm that was established in the coordinator's centre permits doubling of the rate of genetic diagnosis making use of WES, personalised disease models previously established by partner1[8] and an advanced multidisciplinary phenotyping of patients[2,5]. Given the successful application in the coordinator hospital, the public health system of Tuscany has already funded a project to support this diagnostic algorithm for all the patients with NS of the Tuscany region. This diagnostic process reduces the risk of inappropriate treatments and optimizes the choice of drugs[2], enhancing the lifespan of patients and increasing the quality of clinical practice, improving the quality of life of patients and reducing costs for the public health system. From a retrospective model-based cost-efficiency analysis emerges that a personalised genetic diagnosis exhibits a mean cost save. Prospective exploration of ethical, legal, and social aspects of this personalised approach will help further improving the diagnostic algorithm to incorporate patient-related aspects. We think that the EraPerMed program could be the right chance to extend this diagnostic process across Europe, thanks to the implementation strategy here proposed. The management of young patients with NS varies considerably across Europe with a limited access of European patients to benefit from the possibilities of a multidimensional diagnostic work-up leading to a cost-saving personalised care minimizing unnecessary treatment-related morbidity and maximizing renal outcomes before and after kidney transplantation. To spread the access to personalised medicine approach to European centres would lead to cost and time saving that would result in a more rational allocation of resources dedicated to healthcare and research[12] and to additional benefit for all patients affected by NS. This approach can accelerate the translation between mechanistic insights and individualized treatment and improve the performance of diagnosis, prediction, and monitoring of therapeutic response. This will imply a significant impact on clinical decisions and health outcomes, as already proved by the current application across all Tuscany region on a target population of 3.8 million people funded by the local public health system. Our prospective exploration of ethical, legal, and social aspects of this personalised approach will help further improving the diagnostic algorithm to incorporate patient-related aspects. Furthermore, our cost analysis will provide a further argument for decision makers to implement this algorithm to reduce the related health care costs. Altogether, this approach has the potential to implement the highest quality in management of patient with NS across Europe.

3.9. HANDLING OF INTELLECTUAL PROPERTY RIGHTS (E.G. ANY BARRIERS TO SHARING MATERIALS OR RESULTS), BOTH WITHIN AND OUTSIDE THE RESEARCH CONSORTIUM (MAX. ½ PAGE)

Intellectual property rights will be taken into account in order to negotiate any relevant questions with partners before starting the project but no particular barrier to sharing materials or results is foreseen. The pre-existing knowledge that each partner makes available to the other subjects for carrying out the project are the following: 1. The coordinator will perform WES and data analysis according to international protocols. The coordinator and partner1 have previously described and patented (patent number: FI2013A000303) a method for selecting and amplifying RPC from the urine of patients with kidney disease to use for functional genetic tests. Furthermore, partner1 has developed 3D models using specific devices (kidney-on-a-chip). 2. Partner1's team has the knowhow for STED super-resolution microscopy and has already established the scRNAseq technology in collaboration with coordinator. The bioinformatics pipelines required for data analysis are already placed. In case new prognostic biomarkers for the patient outcome may arise from the scRNAseq data, intellectual property will be explored. 3. Partner2 and 3 have already been trained by partner1 to isolate RPC from the urine of patients (see publications). Results will be constantly shared with partners at dedicated web meeting that will be performed monthly and with the scientific community at national and international conferences. They can also be the subject of scientific publications in national and international peer-reviewed journals. In case of patentable results, they will be first evaluated by the coordinator's institution, the Meyer Children's Hospital, that has established a patent unit, which works with the competent regional reference office (Biomedical and Pharmaceutical Research Enhancement Office, UVaR) to manage the processes relating to technology transfer and management of Intellectual property. The patent unit will support the management of intellectual property rights and the economic exploitation of patents. Reference person: Katalin Majer, Promotion and enhancement of research office. https://www.meyer.it/index.php/ricerca-e-innovazione/brevetti.

3.10. DESCRIPTION OF ON-GOING PROJECTS, PENDING PATENTS AND PATENTS WHERE APPLICABLE, OF EACH PARTICIPATING GROUP RELATED TO THE PRESENT TOPIC INDICATING FUNDING SOURCES AND POSSIBLE OVERLAPS WITH PROPOSAL (MAX. 1 PAGE PER GROUP)

Coordinator, Prof. Romagnani P, is a physician scientist with ongoing clinical and research activities. She was the first to identify RPC, the resident kidney stem cells, in adult human kidney. She has characterized the renal progenitor system in adult human kidney and demonstrated its capacity to generate novel podocytes as well as tubular cells of different portions of the nephron, leading to the description of the kidney progenitor system, in human. The discovery of RPC has established an entirely novel view that has changed the way of thinking kidney physiology and pathophysiology. Based on this, she was awarded three ERC grants (2008-2012; 2015-2020; 2021-2026) and has received the Award for Outstanding Contribution to Basic Research in Nephrology by the European Renal Association in 2020. In addition, Paola Romagnani is a clinician that directs the nephrology unit of the Meyer Chiildren's Hospital, a referral center for genetic kidney disorders and member of the European Renal Network (ERN) consortium. She has published several papers about the optimization of genetic diagnosis of patients with NS and has also established a method for selection and identification of RPC from the urine of patients affected by kidney disorders in collaboration with partner1. This method is extremely useful to complement genetic diagnosis of inherited kidney disorders.

On-going project on this topic:

She is coordinator of the project titled "Set-up of a platform for personalized diagnosis of rare kidney diseases" acronym NIKE, granted by Regione Toscana (2020-2023). The project aims to: 1. Propose an integrated diagnostic algorithm to extend novel strategies of personalised diagnosis

and care of rare kidney disorders to all patients <40 years of age with chronic kidney disease (CKD) of the Tuscany region; 2. Promote implementation of personalised diagnosis of CKD with constant update of the panel of genes analyzed in real-time with new causative genes discovery; 3. Support personalised diagnosis with implementation of individual disease modelling 4. Mapping pathways for drug targeting in orphan kidney diseases by single cell RNA sequencing 5. Set-up preclinical gene editing approaches for personalised treatment of selected kidney disorders.

On-going projects as Principal Investigator:

-2019-2024 Associazione Italiana per la Ricerca sul Cancro (AIRC) “Role of renal progenitors and endocycling tubular cells in the pathogenesis of different renal cell carcinoma subtypes”.

-2019-2023 Progetti di Rilevante Interesse Nazionale (PRIN).”New strategies for 3D modelling, diagnosis and treatment of acute kidney injury”

-2021-2026 ERC Advanced Grant 2020-Horizon 2020: “Sexual dimorphism in renal Progenitors to explain gender- specificity in kidney physiology and diseases”. Acronym SIMPOSION. Funded from the European Research Council.

Partner1, Prof. Lazzeri E, is a scientist with a solid expertise in the field of Nephrology Research. Of note, she contributed to identify RPC in adult human kidney. More recently, she demonstrated the existence of a new mechanism of renal response to acute injuries. RPC play an important role in the regeneration of injured tubule segments and hence to the recovery of kidney function after acute kidney injury. Prof. Lazzeri also established and patented a method for selection and identification of RPC from the urine of patients affected by kidney disorders (Patent: Lazzeri E, Lasagni L, Romagnani P. Method for the isolation, purification and amplification of renal progenitors from the urine of patients with kidney disorders. Azienda Ospedaliero Universitaria Meyer. FI2013A000303 del 24/12/2013 patent number 0001421589). This method may allow personalised modelling of kidney disorder and be extremely useful to complement genetic diagnosis of inherited kidney disorders. She collaborated with the coordinator of this project on the role of patient u-RPC as a diagnostic tool to decipher complex genetic forms of NS and with partner3 to decipher lupus nephritis that do not respond to usual immunosuppressive treatments [3,4]. In addition, she has collaborated with partner2 using the isolation method of u-RPC to predict patient prognosis in transplant patients[14].

On-going project on this topic: Lazzeri E is partner of the project titled "Set-up of a platform for personalized diagnosis of rare kidney diseases" acronym NIKE, granted by Regione Toscana.

Partner2, Prof. Cruzado, has 3 on-going projects on this topic:

Bowman's parietal epithelial cells (PECs) and injury/regeneration in kidney transplantation. Identification of innovative therapeutic targets and PEC cell therapy to abrogate ischemia/reperfusion injury (PI15/00638) granted by The Institute of Health Carlos III (ISCIII) from Spanish Ministry of Science, Innovation and Universities. This project is nearly completed. We have compared urinary progenitor kidney cells obtained early after kidney transplantation between living and deceased donor kidney transplant recipients. We identified some epigenetic and transcriptional changes associated with the severity of the ischemia and reperfusion injury that were validated in an independent cohort and now we are finishing some in vitro functional studies to validate the relevance of the molecular findings. There are no patents pending or related with this project. This project is related with the topic but there is not overlap with the current proposal.

RAAS blockade in renal transplant with PECs in urine. randomized clinical trial comparing valsartan with placebo (PI18/00910) granted by The Institute of Health Carlos III (ISCIII) from Spanish Ministry of Science, Innovation and Universities. This clinical trial is recruiting and is based on personalized medicine. The study design was based in previous findings from our group[14] showing the association between the presence of kidney progenitor cells in urine 6 months after kidney transplantation and mid-term kidney allograft deterioration. Our hypothesis is that glomerular hypertension promotes the presence of renal progenitor cells in the urine of stable kidney allograft recipients RAAS blockade by valsartan in these patients at risk could reduce glomerular

hypertension and improve prognosis. There are no patents pending or related with this project. This project is related with the topic but there is not overlap with the current proposal.

Macrophage stimulating factor as key regulator of kidney progenitor cell (PI17/01411) granted by The Institute of Health Carlos III (ISCIII) from Spanish Ministry of Science, Innovation and Universities. In this study we are investigating the role of macrophage colony stimulating factor (M-CSF) in some experimental models of glomerular diseases such as Focal and Segmental Glomerulosclerosis (FSGS) and extracapillary glomerulonephritis. We generated relevant data in vitro and in vivo showing that M-CSF is a relevant regulator of kidney progenitor cell function and crosstalk between kidney progenitor cells and podocytes. This project is nearly completed and we are finishing some validation studies. There are no patents pending or related with this project. This project is related with the topic but there is not overlap with the current proposal.

Partner3 Prof. HJ Anders is a physician scientist with ongoing clinical and research activities. Clinically, he has specific expertise on the various forms of glomerular forms of kidney injury, i.e., glomerulonephritis, in adults. Expertscape.com, a global expert ranking platform, ranks him 3. for glomerulonephritis and first for Europe. His special clinical focus are patients with systemic lupus erythematosus and lupus nephritis (Expertscape global rank 1). HJA is a regular speaker on interdisciplinary international conferences on lupus and is active to generate progress in how to personalize diagnosis and treatment of lupus nephritis more efficiently. An ongoing project, together with other European partners, is the ReBioLup trial that tries to personalize maintenance treatment of lupus nephritis on the basis of a protocol biopsy performed one year after the first biopsy (http://rebiolup.com/). HJA has collaborated with the coordinator of this project on the role of patient u-RPC as a diagnostic tool to decipher complex genetic forms of lupus nephritis that do not respond to usual immunosuppressive treatments.[4] The Renal Division at LMU, which he directs at the Inner-City Campus, is a very active recruitment site for numerous clinical trials on the different forms of glomerular injury (LN, IgAN, DKD, TMA, AAV). However, none of the ongoing and foreseen trials would be in conflict with the planned ERA-PerMed project on patients with NS. For this project HJA will collaborate with Dr. Bärbel Lange-Sperandio, the head of the pediatric nephrology unit at LMU, to accelerate patient recruitment as NS is more prevalent in children with kidney disease. B.L-S has included patients with NS into previous multicentre trials but run no such trial for the foreseeable future that would be in conflict with the planned ERA-PerMed project.

A particular strength of the nephrology units at LMU is the connection of clinical with molecular research on the pathophysiology of kidney disease. HJA holds a Heisenberg research professorship supported by the Deutsche Forschungsgemeinschaft on “Inflammatory mechanisms of nephron loss”. Indeed, HJA`s group works for 20 years on translational aspects of various forms of kidney disease including glomerulonephritis and glomerulosclerosis with a special focus on the role of the innate immune system. Ongoing projects include the role canonical and non-canonical roles of the NLRP3 inflammasome, the molecular mechanisms of immunothrombosis and crystal nephropathies and the cell type-specific mechanisms of nucleoprotein HMGB1. HJA collaborates with the coordinator of this project on the role of RPC in kidney regeneration. A recent project described a previously unknown podocyte-progenitor feedback mechanism that can be modulated with drug interventions to accelerate podocyte regeneration and prevent CKD progression in mice.[15] In another recent project, we described how to enhance podocyte regeneration and control proteinuria with drugs beyond RAS/SGLT2 blockade in diabetic kidney disease.[7] Ongoing joined projects address other exciting perspectives for the understanding and treatment of glomerular forms of chronic kidney disease. HJA is currently funded by the German Research Foundation with none of the projects overlapping with the proposal presented here. The group of B-L.S. works on the molecular mechanisms of neonatal obstructive nephropathy, which is unrelated to this project.

3.11. PATIENT INVOLVEMENT (MAX. ½ PAGE)

Please provide information about the involvement/contribution of relevant patient organisations and patient representatives within the proposal (if available/applicable).

The coordinator has a constant cross talk with Italian organizations of patients with NS (ASNIT Onlus, www.asnit.org, Fondazione la Nuova Speranza Onlus, www.lanuovasperanza.org). The involvement of patient organisations will be helpful to diffuse information among patients about the existence and the application in the centre of coordinator of a personalised diagnostic algorithm. This algorithm reduces the risk of inappropriate treatments and optimizes the choice of drugs[2], enhancing the lifespan of patients and increasing the quality of clinical practice, improving the quality of life of patients and reducing costs for the public health system. *Vice versa*, personal experience of patients can be helpful to identify which aspects (global health, social interactions) display a major impact in quality of life, improving the analysis of clinical consequences of the proposed diagnostic algorithm. Thus, the involvement of patient organisations will support feedback on the algorithm and its effect on the quality of life at national level and ethical to better involve patients in all stages of the process.

3.12. INCLUSION OF GENDER AND/OR SEX ANALYSIS (MAX. ½ PAGE)

Please provide information about the consideration of sex aspects in research teams and the inclusion of sex and/or gender analysis in the research, if applicable.

The consortium is well balanced in terms of gender of principal investigators and their teams (50:50). This is helpful also for a balanced interpretation of the data since it is known that the sex of the researcher has a potential impact on balanced recruitment of research participants. In addition, the consortium has a female as a coordinator and it was previously reported that in biomedical, clinical and public health research, women in leading positions (first and last author) are more likely to analyze sex and gender in published research[16,17]. Since ignoring sex and gender analysis can lead to inaccuracies, research inefficiency and difficulties generalizing results, we plan to perform descriptive statistical analyses of the results based on different genders of the different types of genetic diagnoses, responses to treatment, prognosis of the recruited patients. In addition, we will apply scRNAseq analysis in both male and female patients to select potential biomarkers for prediction of patient outcome also taking sex into account (see WP3). To this aim, we will prepare a list of all the potential biomarkers that are differentially regulated in males and females for their analysis and validation. *In vitro* and *in vivo* validation will be performed on cultures and biopsies of different gender.

3.13. ETHICAL ISSUES OF THE PROJECT PROPOSAL (MAX. ½ PAGE)

Please address ethical, safety and legal issues (e.g. informed consent, patient data protection, ethical permits, data protection, and use of animal, if available/applicable) according to national regulations. If there are none to address, please explain why.

Proposals including a Clinical Study must include as an Annex the duly filled out form for "Exploratory Clinical Studies" *(template available* as Annex I to this document*).*

Patients who consent to participate in the study will be informed in detail of all the research activities that will be carried out with the data collected, as reported in the informed consent. The latter will then be collected from the patient or their legal tutor prior to be enrolled. All patients will be asked for informed consent to collect a blood sample, one or more urine samples and to use the kidney biopsy, already performed for diagnostic purposes. In particular, to allow the correct segregation of identified variants, a blood sample will also be required by the patient's parents. Genetic analysis may be extended to other affected family members (e.g. siblings) based on the family history of the disease. The identity, as well as any other type of information concerning the

patient, will be treated as strictly confidential, therefore a procedure to ensure anonymity of data will be applied. Each enrolled patient will be assigned an alpha-numeric code that will allow the pseudo-anonymization. After anonymization procedure, patients will be registered in an eCRF. The decryption file will be stored in a secure locker and it will only be accessible to the coordinator and the partners involved in the study. The coordinator will create a multicentre database with patient information and the results of the study, which will be shared with the other partners. Ethical, safety and legal issues of the study has already be submitted to the Local Ethics Committee by coordinator, according to national regulations. The study will be conducted in accordance with the rules of good clinical practice (GCP), the ethical principles deriving from the Declaration of Helsinki and current legislation on observational studies. The coordinator is in possession of the GCP-R2 certificate and will be requested from all partners not yet in possession to get it before starting the study. The study will start only after obtaining the favorable opinion of the Regional Ethics Committee.

3.14. DATA MANAGEMENT STRATEGY/PLAN[1] (MAX. 2 PAGE)

Description of how the research data in this project will be findable, accessible, interoperable and re-usable: the handling of research data during & after the end of the project; what data will be collected, processed and/or generated and/or reused; which methodology & standards will be applied; whether data will be shared/made open access; how data will be curated & preserved. ***In this section, the Data Management Plan (DMP) must be outlined in brief.***

Consortia of projects selected for funding must submit a more detailed DMP (template will be provided to the respective consortia).

The Data Management plan (DMP) aims at providing a timely insight into facilities and expertise necessary for data management both during and after the project is finished, to be used by all partners. The most important reasons for setting up this DMP are:

• Embedding the project in the EU policy on data management. The rationale is that the EraPerMed grant consists of public money and therefore the data should be accessible to other researchers;

• Enabling verification of the research results of the project;

• Stimulating the reuse of the data by other researchers;

• Enabling the sustainable and secure storage of data in repositories;

It is important to note however that the DMP can evolve and further develop during the project's life cycle.

Upon obtaining the informed consent for participation in the study, Personal, clinical, laboratory and instrumental data will be collected by specialists in nephrology involved in the project by the coordinator, and specifically trained. The information will be obtained from the patient's medical record, paper or computerized, at the date of enrolment, with the help of an eCRF.

The most common information of interest will include, as appropriate:

- Clinical variables: age, sex, physiological, past and proximate medical history, weight, height, BMI, body surface area, blood pressure, ongoing medical therapy, birth weight;

- Laboratory tests: blood count, creatinine, BUN, sodium, potassium, chloride, calcium, phosphorus, PTH, total protein, electrophoretic profile, complement factors (C3, C4), immunoglobulins, autoimmunity profile, blood gas analysis, urinalysis, 24 hour proteinuria, urinary protein/creatinine ratio, urinary calcium/creatinine ratio, urinary pH, urinary protein profile;

[1] For more information please consult:
http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf

- Instrumental examinations: abdomen ultrasound, kidney biopsy, bone age x-ray, chest x-ray, abdomen CT or MRI, brain CT or MRI, voiding cystography, sequential renal scintigraphy, uroflowmetry, audiometry.

All patients will be asked for informed consent for the collection of a blood sample, one or more urine samples and for the use of renal biopsy, already performed for diagnostic purposes. The sampling will always involve the patient and both parents, subject to their informed consent, in order to correctly establish the segregation of the variants. The analysis may possibly be extended to brothers and / or sisters of the patient likely suffering from the kidney disease under study. In cases where an inconclusive result is obtained from the genetic analysis and / or if deemed necessary by the coordinating centre of the study, the following will be performed to complete the diagnosis:

- further laboratory and instrumental investigations on the basis of the diagnostic suspicion suggested by the variant identified (e.g. renal biopsy; audiometric and impedance analysis in a patient with suspected Alport syndrome; urinary protein profile in a patient with suspected tubulopathy) (reverse phenotyping) in order to understand its role in the pathogenesis of the disease;

- functional analysis of VUS on cultures of RPC isolated from the patient's urine;

- Personalised detection of immunologic factors and circulating permeability factors by using STED super-resolution analysis and 3D organ-on-a-chip;

-scRNAseq analysis of u-RPC for biomarker identification and to predict patient outcome.

All the above information, once anonymized, will be included in the multicentre database and shared among partners. The database has a well-defined structure and documentation of all variables. All data of the proposal are coded according to the EU policy on data management. The information contained in the database will be inaccessible to unauthorized persons. It will also be possible to obtain a descriptive statistical analysis of the characteristics of the population enrolled in the study, in order to obtain information such as:

- the prevalence of genetic diagnoses in the study population;

- the number of new diagnoses (by using reverse phenotyping, by detecting immunologic and circulating permeability factors);

- prediction of patient outcome by biomarker identification;

The digital data will be stored on a local server within the Meyer Children’s Hospital, Bellvitge Biomedical Research Institute and LMU Klinikum, which will provide password protection and safe storage of confidential data. In addition, data will be curated and preserved in a common repository for open-data that is easily accessible by partners, to verify the results of scientific research, and to manage the data appropriately. This will enable coordinator, partner1, partner2 and partner3 to find and get access to the data. Coordinator and partners will ensure that all clinical data will be stored in accordance with the principles of GCP as defined by the International Conference of Harmonisation (ICH)/WHO standards and national regulatory requirements. Following publication all data will be made available at public repositories. Long-term storage will be performed for a minimum of 10 years after publication.

4. IN ADDITION, TWO MORE PAGES CAN BE ADDED TO THE FULL-PROPOSAL (OPTIONAL):

- List of references (max. 1 page)
- A letter of commitment for a partner not eligible to be funded by one of the organisations participating in this JTC2021 but participating with its own resources: a signed statement must be included as an Annex to the full-proposal summarising the commitment of this partner to the project and demonstrating its source of funding. (max. 1 page).

List of references:

1) Kopp JB*, Anders HJ*, et al. Podocytopathies. Nat Rev Dis Primers. 2020; 6:68.

2) Landini S, et al. Reverse Phenotyping after Whole-Exome Sequencing in Steroid-Resistant Nephrotic Syndrome. Clin J Am Soc Nephrol. 2020; 15:89-100.

3) Lazzeri E, et al. Human Urine-Derived Renal Progenitors for Personalized Modeling of Genetic Kidney Disorders. J Am Soc Nephrol. 2015; 26:1961-1974

4) Romagnani P, et al. Next generation sequencing and functional analysis of patient urine renal progenitor-derived podocytes to unravel the diagnosis underlying refractory lupus nephritis. Nephrol Dial Transplant. 2016; 31:1541-1545.

5) Becherucci F, et al. Look Alike, Sound Alike: Phenocopies in Steroid-Resistant Nephrotic Syndrome. Int J Environ Res Public Health. 2020; 17:8363.

6) Peired AJ, et al. Acute kidney injury promotes development of papillary renal cell adenoma and carcinoma from renal progenitor cells. Science Translational Medicine. 2020; 12:eaaw6003.

7) Motrapu M, et al. Drug Testing for Residual Progression of Diabetic Kidney Disease in Mice Beyond Therapy with Metformin, Ramipril, and Empagliflozin. J Am Soc Nephrol. 2020; 31:1729-1745.

8) Giglio S, et al. Heterogeneous genetic alterations in sporadic nephrotic syndrome associate with resistance to immunosuppression. J Am Soc Nephrol. 2015; 26:230-236.

9) Doimo M, et al. Effect of vanillic acid on COQ6 mutants identified in patients with coenzyme Q10 deficiency. Biochim. Biophys Acta. 2014; 1842:1–6.

10) Kienzl-Wagner K, et al. Successful management of recurrent focal segmental glomerulosclerosis. Am. J. Transpl. 2018; 18:2818–2822.

11) Kashgary A, et al. The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis: a systematic review and meta-analysis of 77 case-reports and case-series. BMC Nephrol. 2016; 17:104.

12) O'Donnell JC. Personalized Medicine and the Role of Health Economics and Outcomes Research: Issues, Applications, Emerging Trends, and Future Research. Value in Health. 2013; 16:s1-s3.

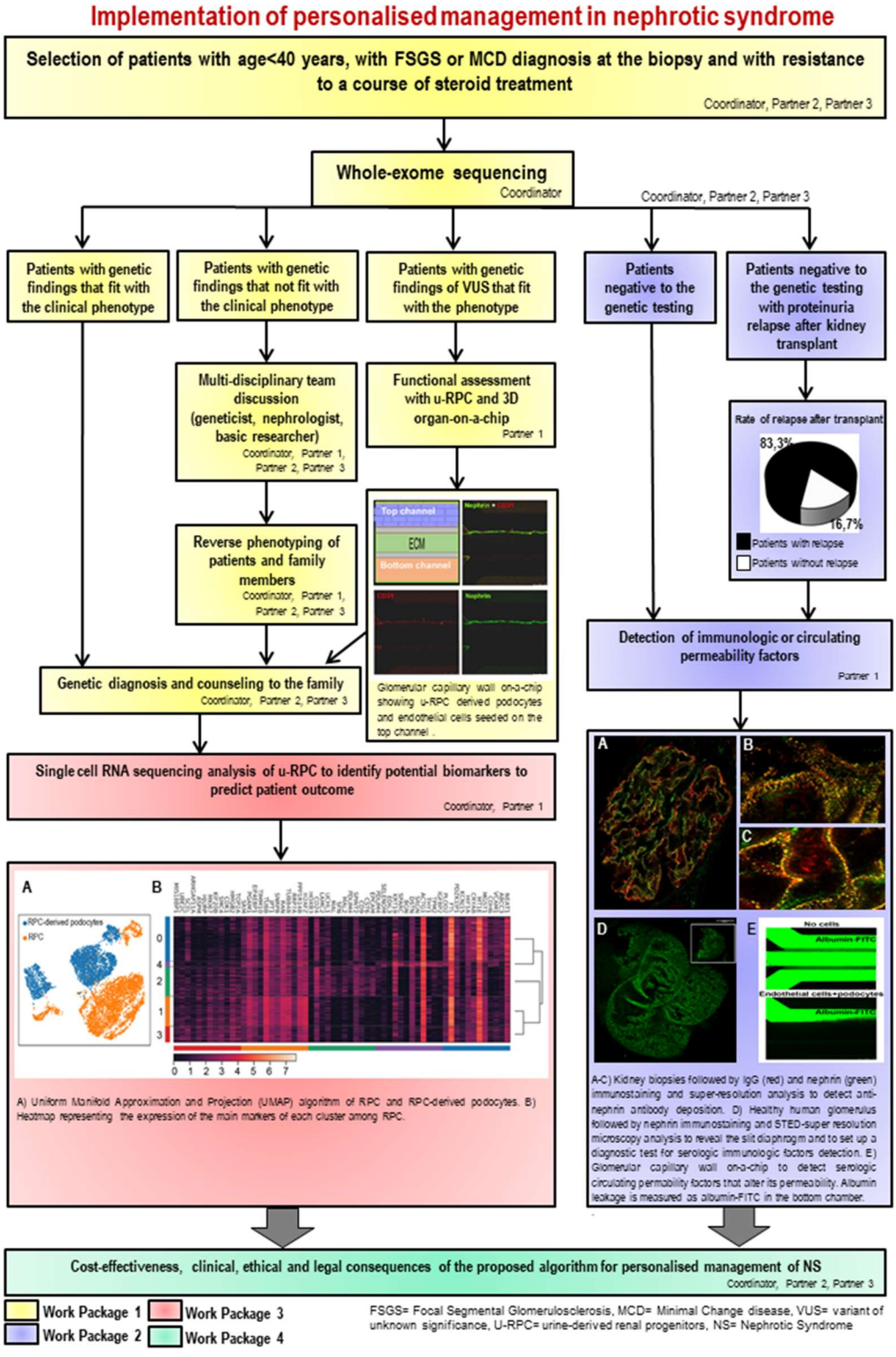
13) Fine RN. Recurrence of nephrotic syndrome/focal segmental Glomerulosclerosis following renal transplantation in children. Pediatr Nephrol. 2007; 22:496-502.

14) Manonelles A, et al. The presence of urinary renal progenitor cells in stable kidney transplant recipients anticipates allograft deterioration. Frontiers in Physiology. 2018; 9:1412.

15) Romoli S, et al. CXCL12 blockade preferentially regenerates lost podocytes in cortical nephrons by targeting an intrinsic podocyte-progenitor feedback mechanism. Kidney Int.2018; 94:1111-1126.

16) Nielsen MW, et al. One and a half million medical papers reveal a link between author gender and attention to gender and sex analysis. Nat. Hum. Behav. 2017; 1, 791–796.

17) Sugimoto CR, et al. Factors affecting sex- related reporting in medical research: a cross-disciplinary bibliometric analysis. Lancet 2019; 393, 550–559.


Implementation of personalised management in nephrotic syndrome
Selection of patients with age<40 years, with FSGS or MCD diagnosis at the biopsy and with resistance to a course of steroid treatment
Coordinator, Partner 2, Partner 3
Whole-exome sequencing
Coordinator
Coordinator, Partner 2, Partner 3
Patients with genetic findings that fit with the clinical phenotype
Patients with genetic findings that not fit with the clinical phenotype
Patients with genetic findings of VUS that fit with the phenotype
Patients negative to the genetic testing
Patients negative to the genetic testing with proteinuria relapse after kidney transplant
Multi-disciplinary team discussion (geneticist, nephrologist, basic researcher)
Coordinator, Partner 1, Partner 2, Partner 3
Functional assessment with u-RPC and 3D organ-on-a-chip
Partner 1
Rate of relapse after transplant
83,3%
16,7%
Patients with relapse
Patients without relapse
Reverse phenotyping of patients and family members
Coordinator, Partner 1, Partner 2, Partner 3
Top channel
ECM
Bottom channel
Glomerular capillary wall on-a-chip showing u-RPC derived podocytes and endothelial cells seeded on the top channel .
Genetic diagnosis and counseling to the family
Coordinator, Partner 2, Partner 3
Detection of immunologic or circulating permeability factors
Partner 1
Single cell RNA sequencing analysis of u-RPC to identify potential biomarkers to predict patient outcome
Coordinator, Partner 1
A
B
RPC-derived podocytes
RPC
A) Uniform Manifold Approximation and Projection (UMAP) algorithm of RPC and RPC-derived podocytes. B) Heatmap representing the expression of the main markers of each cluster among RPC.
A
B
C
D
E
No cells
Albumin-FITC
Endothelial cells+podocytes
Albumin-FITC
A-C) Kidney biopsies followed by IgG (red) and nephrin (green) immunostaining and super-resolution analysis to detect anti-nephrin antibody deposition. D) Healthy human glomerulus followed by nephrin immunostaining and STED-super resolution microscopy analysis to reveal the slit diaphragm and to set up a diagnostic test for serologic immunologic factors detection. E) Glomerular capillary wall on-a-chip to detect serologic circulating permability factors that alter its permeability. Albumin leakage is measured as albumin-FITC in the bottom chamber.
Cost-effectiveness, clinical, ethical and legal consequences of the proposed algorithm for personalised management of NS
Coordinator, Partner 2, Partner 3
Work Package 1
Work Package 2
Work Package 3
Work Package 4
FSGS= Focal Segmental Glomerulosclerosis, MCD= Minimal Change disease, VUS= variant of unknown significance, U-RPC= urine-derived renal progenitors, NS= Nephrotic Syndrome

5. FINANCIAL PLAN OF PROJECT BUDGET (IN €[1]): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

*Please note that **not** all types of expenditure are fundable by all funding organisations (see the "Guidelines for Applicants" for details on the eligibility criteria and/or contact the relevant ERA PerMed regional/national funding organisation). Thousand separators and whole numbers should be used only (e.g. 200.000).*

Partners	**Coordinator**		**Partner 1**		**Partner 2**		**Partner 3**		**Partner 4**		**Partner 5**		**Partner 6**			
Name (group leader)	**Paola Romagnani**		**Elena Lazzeri**		**JM Cruzado**		**Hans-J. Anders**									
Institution	**Meyer Children's Hospital**		**University of Florence**		**IDIBELL**		**LMU Klinikum**									
Country	**Italy**		**Italy**		**Catalonia (Spain)**		**Germany**									
Funding organisation	**Tuscany region**		**Tuscany region**		**DS-CAT**		**BMBF**									
PROJECT COSTS (€)	**Total cost**	**Requested**	**Total cost**	**Requested**	**Total cost**	**Requested**	**Total cost**	**Requested**	**Total cost**	**Requested**	**Total cost**	**Requested**	**Total cost**	**Requested**	**Total**	**Requested**
Personnel €	**171.312**	**75.000**	**172.190**	**75.000**	**162.187**	**125.017**	**229.800**	**132.300**								
Consumables €	**72.000**	**72.000**	**40.000**	**40.000**	**35.000**	**25.000**	**32.000**	**32.000**								
Equipment €	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**								
Travel €[2]	**0**	**0**	**0**	**0**	**3.000**	**3.000**	**3.000**	**3.000**								
Other direct costs €[3]	**8.000**	**8.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**								
Overheads €[4]	**15.000**	**15.000**	**10.000**	**10.000**	**31.603**	**31.603**	**53.960**	**34.460**								
Subcontracting	**0**	**0**	**0**	**0**	**2.500**	**2.500**	**0**	**0**								
Total	**266.312**	**170.000**	**227.190**	**130.000**	**239.920**	**192.120**	**323.760**	**206.760**								

[1] Those countries whose currency is different than € shall include their national currency in brackets.
[2] Please bear in mind that coordinators (and partners) shall present the projects at a midterm or final ERA PerMed symposium.
[3] E.g. provisions, licensing fees; may not be eligible costs in all countries (will be handled according to regional/national regulations).
[4] Overhead costs: funding according to regional/national regulations.

5.1. FINANCIAL PLAN OF THE COORDINATOR - (IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total cost	Requested
Personnel *Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)*	OWN FUNDING: 1 Full professor and 1 Staff Physician for clinical data collection and analysis, 1 Staff Biologist for genetic data analysis (18 total months for € 96.312,5). ON FUNDING: 2 fixed-term contracts for whole exome and scRNA sequencing (36 total months, € 75.000,0).	**€ 171.312**	**€ 75.000**
Consumables *Please specify (e.g. reagents, kits, antibodies, cell culture material, animals, etc.)*	Kits for whole exome sequencing and scRNA sequencing	**€ 72.000**	**€ 72.000**
Equipment *Please specify equipment*	Not required	**0**	**0**
Travel *Please specify (e.g. allowances, meeting fees, etc.)*	Not required	**0**	**0**
Other Direct Costs *Please specify (e.g. animal costs, provisions, licensing fees, patents, publications, etc.)*	Two open access publications	**€ 8.000**	**€ 8.000**
Overheads*	Tuscany Region: overhead maximum 10%	**€ 15.000**	**€ 15.000**
Subcontracting	Not required	**0**	**0**
	Total	**€ 266.312**	**€ 170.000**

* Please note that there is no common flat rate for the overheads category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for Applicants" or contact your relevant funding agency for further information.

5.2. FINANCIAL PLAN OF PROJECT PARTNER 1 (IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total cost	Requested
Personnel *Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)*	OWN FUNDING: 2 Associate Professors for data analysis, 1 Technician for confocal microscopy and a STED-super resolution microscopy (20 total months, € 97.190,0). ON FUNDING: 1 fellowship for renal progenitor isolation, 3D organ-on-a-chip assay and scRNA library preparation (24 months, €25.000/year), 1 fellowship for bioinformatic analysis (12 months, €25.000/year).	**€172.190**	**€75.000**
Consumables *Please specify (e.g. reagents, kits, antibodies, cell culture material, animals, etc.)*	Cell culture material, 3D organ-on-a-chip, reagents for confocal and STED microscopy, kits for scRNA library preparation.	**€40.000**	**€40.000**
Equipment *Please specify equipment*	Not required	**0**	**0**
Travel *Please specify (e.g. allowances, meeting fees, etc.)*	Not required	**0**	**0**
Other Direct Costs *Please specify (e.g. animal costs, provisions, licensing fees, patents, publications, etc.)*	One open access publication	**€5.000,0**	**€5.000,0**
Overheads*	Tuscany Region: overhead maximum 10%	**€10.000,0**	**€10.000,0**
Subcontracting	Not required	**0**	**0**
	Total	**€ 227.190**	**€ 130.000**

* Please note that there is no common flat rate for the overheads category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for Applicants" or contact your relevant funding agency for further information.

5.3. FINANCIAL PLAN OF PROJECT PARTNER 2(IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total cost	Requested
Personnel *Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)*	One postDoc researcher full-time dedication for three years (36 Person-Months) that will be in charge of the collection and process of cell cultures, and to perform and export project data is required. Two clinical investigators with part time dedication (10 and 5 Person-Month) will be in charge of the obtention of informed consent and clinical and analytical data collection, as well as further data evaluation (their costs are not required)	**€162.817**	**€125.017**
Consumables *Please specify (e.g. reagents, kits, antibodies, cell culture material, animals, etc.)*	Cell culture material: media (EGM-MV), FBS, antibiotics, reagents, antibodies for FACs CANTO (partially covered by previous grants). Kits for whole exome sequencing.	**€35.000**	**€25.000**
Equipment *Please specify equipment*	Not required	**0**	**0**
Travel *Please specify (e.g. allowances, meeting fees, etc.)*	Travel for consortium meetings and presentations of results in Congresses	**€3.000**	**€3.000**
Other Direct Costs *Please specify (e.g. animal costs, provisions, licensing fees, patents, publications, etc.)*	Sample shipment. Publication costs (covered by previous grants)	**€5.000**	**€5.000**
Overheads*	20% of direct costs excluding subcontracting, as defined by DS-CAT	**€31.603**	**€31.603**
Subcontracting	Financial audit certificate	**€2.500**	**€2.500**
	Total	**€239.920**	**€192.120**

* Please note that there is no common flat rate for the overheads category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for Applicants" or contact your relevant funding agency for further information.

5.4. FINANCIAL PLAN OF PROJECT PARTNER 3(IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total cost	Requested
Personnel *Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)*	One lab technician (27 PM) urine sampling and processing, cell culture and assays, data analysis and exportation One clinician (12 PM) for informed consent, clinical data collection covered by institution	**€229.800**	**€132.300**
Consumables *Please specify (e.g. reagents, kits, antibodies, cell culture material, animals, etc.)*	Cell culture material: media (EGM-MV), FBS, antibiotics, reagents, biochemical, antibodies for FACS CANTO in order to execute tasks, bioassays, plastic and glass ware. Kits for whole exome sequencing.	**€32.000**	**€32.000**
Equipment *Please specify equipment*	Not required	**0**	**0**
Travel *Please specify (e.g. allowances, meeting fees, etc.)*	Travel for consortium meetings and presentations of results in Congresses	**€3.000**	**€3.000**
Other Direct Costs *Please specify (e.g. animal costs, provisions, licensing fees, patents, publications, etc.)*	User fees for centralized FACS sorting service and bioimaging unit Sample shipment costs, publication fees	**€5.000**	**€5.000**
Overheads*	BMBF overhead of 20%	**€53.960**	**€34.460**
Subcontracting	Not required	**0**	**0**
	Total	**€323.760**	**€206.760**

* Please note that there is no common flat rate for the overheads category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for Applicants" or contact your relevant funding agency for further information.

6. BRIEF CVS OF CONSORTIUM PARTNERS

For each of the consortium partners, please provide a brief CV for the Project Consortium Coordinator and each Project Partner's Principal Investigator with a list of up to five relevant publications within the last five years demonstrating how he/she is suitably qualified and experienced to carry out the project (max. 1 page each, complete form below).

6.1. COORDINATOR

Last Name	Romagnani
First Name	Paola
Institution	Meyer Children's Hospital
Short CV	Date of birth: 02/03/1970 ORCID ID: 0000-0002-1774-8088 **CURRENT POSITION** Full Professor and Chair of Nephrology/University of Florence/Italy Head of Nephrology and Dialysis Unit, Meyer Children's Hospital, Florence. **Academic Degrees** 1995: Degree in Medicine and Surgery/Faculty of Medicine and Surgery/University of Florence. 2001: PhD in Endocrinology and Metabolism/Department of Clinical Pathophysiology/University of Florence. 2004: Specialization in Nephrology/Dialysis and Transplantation/Department of Internal Medicine/University of Florence. **Previous Appointments** 2002–2006: Researcher in Nephrology/Department of Clinical Pathophysiology/University of Florence. 2006– 2015: Associate Professor of Nephrology/Department of Clinical Pathophysiology/University of Florence. **Institutional responsabilities** 2009 – 2019: Director of the Specialty School in Nephrology/University of Florence/Italy **Research Topics** -Identification of the renal progenitor system in adult human kidney. -Personalised modelling of kidney disorder. **Competitive Grants as Principal Investigator** 2021: ERC Advanced Grant Investigator Award 2020: National project Bando Ricerca Salute 2018, "Set-up of a platform for personalized diagnosis of rare kidney diseases" acronym NIKE. 2015:ERC Consolidator Grant Investigator Award 2008:ERC Starting Grant Young Investigator Award
List of five relevant publications within the last five years	**Total number of publications: 205, H-Index: 78, Total citations: >21000** 1 Kopp JB*, Anders HJ*, et al.; **Romagnani P**. Podocytopathies. Nat Rev Dis Primer. 2020; 6:68 2. Peired AJ, et al., **Romagnani P**. Acute kidney injury promotes development of papillary renal cell adenoma and carcinoma from renal progenitor cells. Science Translational Medicine. 2020; 12:eaaw6003. 3. Landini S, et al., **Romagnani P**. Reverse Phenotyping after Whole-Exome Sequencing in Steroid-Resistant Nephrotic Syndrome. Clin J Am Soc Nephrol. 2020; 15: 89-100. 4. Romoli S, et al., Anders HJ*, **Romagnani P***. CXCL12 blockade preferentially regenerates lost podocytes in cortical nephrons by targeting an intrinsic podocyte-progenitor feedback mechanism. Kidney Int. 2018; 94:1111-1126. 5. **Romagnani P**, et al. Next generation sequencing and functional analysis of patient urine renal progenitor-derived podocytes to unravel the diagnosis underlying refractory lupus nephritis. Nephrol Dial Transplant. 2016; 31:1541-1545.

6.2. PROJECT PARTNER 1

Last Name	Lazzeri
First Name	Elena
Institution	University of Florence
Short CV	Date of birth: 06/12/1974 ORCID ID: 0000-0002-9505-2115 **CURRENT POSITION** 2017: Associate Professor in Technical Sciences of Laboratory Medicine at the University of Florence, Department of Experimental and Clinical Biomedical Sciences. **Academic Degrees** 1999: Degree on Biological Sciences at the University of Florence. 2003: Specialization in Biochemistry and Clinical Chemistry at the School of Medicine, University of Florence. **Previous Appointments** 2003: Post-doctoral researcher at the Department of Internal Medicine, University of Florence. 2005: Researcher in Technical Sciences of Laboratory Medicine at the Department of Internal Medicine, University of Florence. **Academic/Medical functions** 2013/2014: Teacher at the School of Specialization of Nephrology and Allergology and Immunology, University of Florence. 2019/2020: Teacher at the School of Specialization of Clinical Biochemistry and clinical Pathology and Anatomic Pathology, University of Florence. **Research Topics** -Identification of renal progenitors in adult human kidney and their role in kidney regeneration. -Personalised modelling of kidney disorder **Grants** -2020: Principal Investigator of the Research Unit of the national project Bando Ricerca Salute 2018, with the study titled "Set-up of a platform for personalized diagnosis of rare kidney diseases" acronym NIKE.
List of five relevant publications within the last five years	**Total number of publications: 68, H-Index: 40, Total citations: 6835** 1. Peired AJ, et al., **Lazzeri E**. Bioengineering strategies for nephrologists: kidney was not built in a day. Expert Opin Biol Ther. 2020; 23:1-14. 2. Peired AJ, et al. Acute kidney injury promotes development of papillary renal cell adenoma and carcinoma from renal progenitor cells. Science Translational Medicine. 2020; 12:eaaw6003. 3. Manonelles A, et al. The presence of urinary renal progenitor cells in stable kidney transplant recipients anticipates allograft deterioration. Frontiers in Physiology. 2018; 9:1412. 4. **Lazzeri E**, et al. Endocycle-related tubular cell hypertrophy and progenitor proliferation recover renal function after acute kidney injury. Nat Comm. 2018; 9:1344. 5. Romagnani P, et al., **Lazzeri E**, Anders HJ. Next generation sequencing and functional analysis of patient urine renal progenitor-derived podocytes to unravel the diagnosis underlying refractory lupus nephritis. Nephrol Dial Transplant. 2016; 31:1541-1545.

6.3. PROJECT PARTNER 2

Last Name	Cruzado
First Name	Josep Maria
Institution	Bellvitge Biomedical Research Institute (IDIBELL)
Short CV	Date of birth: 25/03/1965 ORCID ID: 0000-0003-1388-8558 2019-…….. Full Professor of Nephrology, University of Barcelona 2015-…….. Head, Nephrology Department, Bellvitge University Hospital 2015-…….. Associate Editor, Clinical Kidney Journal 2015-…….. Associate Editor, American Journal of Transplantation 2016-2020 President, Catalan Society of Nephrology 2015-2018 President, Research Committee, Bellvitge University Hospital 2013-2018 Board Member of Diabesity, ERA-EDTA working group 2012-2015 Head, Kidney Transplant Unit, Bellvitge University Hospital 2012-2014 Coordinator, Kidney Transplant Group, Spanish Society Nephrology 2009-2019 Associate Professor of Medicine, University of Barcelona 2008-2014 Research Coordinator, Spanish Society of Nephrology 2001-2012 Nephrologist, Bellvitge University Hospital 1995-2000 Medical Thesis Doctorate, University of Barcelona 1991-1994 Nephrology Fellowship, Bellvitge University Hospital 1983-1989 Medical School at University of Barcelona, MD degree
List of five relevant publications within the last five years	**Total number of publications: 394, H-Index: 43, Total citations: 6.009** 1.Berchtold L; Letouzé E; Alexander MP; Canaud G; Logt AV; Hamilton P; Mousson C; Vuiblet V; Moyer AM; Guibert S; Mrázová P; Levi C; Dubois V; **Cruzado JM**; Torres A; Gandhi MJ; Yousfi N; Tesar V; Viklický O; Hourmant M; Moulin B; Rieu P; Choukroun G; Legendre C; Wetzels J; Brenchley P; Ballarín Castan JA; Debiec, H; Ronco P. HLA-D and PLA2R1 risk alleles associate with recurrent primary membranous nephropathy in kidney transplant recipients. Kidney Int. 2020; S0085-2538-20:30967-30974. 2. Narváez A, et al., **Cruzado JM**. siRNA-silencing of CD40 attenuates unilateral obstruction-induced kidney injury in mice. Plos One. 2019; 14:e0215232. 3. Manonelles A, et al., **Cruzado JM**. The presence of urinary renal progenitor cells in stable kidney transplant recipients anticipates allograft deterioration. Frontiers in Physiology. 2018; 9:1412. 4. **Cruzado JM,** et al. Paricalcitol versus calcifediol for treating hyperparathyroidism in kidney transplant recipients. Kidney Int Reports. 2017; 3:122-132. 5. **Cruzado JM,** et al. A Randomized Study Comparing Parathyroidectomy with Cinacalcet for Treating Hypercalcemia in Kidney Allograft Recipients with Hyperparathyroidism. J Am Soc Nephrol. 2016; 27:2487-2494.

6.4. PROJECT PARTNER 3

Last Name	Anders
First Name	Hans-Joachim
Institution	University Hospital of Ludwig-Maximilians University Munich (LMU Klinikum)
Short CV	Date of birth: 04/04/1967 ORCID ID: 0000-0003-2434-2956 2019- Full Professor of Nephrology 2018 ERA-EDTA Award for Outstanding Basic Science Contributions to Nephrology 2017 West European Regional Board, Intern. Society of Nephrology 2016- Associate Editor J Am Soc Nephrol, Nephrol Dial Transplant 2014- Scientific Advisory Board, ERA-EDTA 2008- Professor, Head of Nephrology and of Kidney Research Institute, Inner City Campus, Univ. of Munich (LMU) 2004 Consultant nephrologist, Nephrology Center, Univ. of Munich, 2003 Habilitation, Assistant professor ('Privatdozent') 2001-2005 German boards in internal medicine (2001), nephrology (2002), rheumatology (2005) 1995 Clinical training and nephrology fellowship, Med. Poliklinik, Univ. of Munich (mentor: Detlef Schlöndorff, M.D.) 1995 Medical thesis doctorate (Dr. med.), Univ. of Würzburg 1994 German Academic Exchange, Univ. of Canberra, Australia 1988-1994 Medical School at the Univ. of Göttingen (1988-90) and Würzburg (1990-94), MD federal state exam
List of five relevant publications within the last five years	**Total number of publications: 358, H-Index: 84 , Total citations: >22000** 1: Kopp JB*, **Anders HJ*,** Susztak K, Podestà MA, Remuzzi G, Hildebrandt F, Romagnani P. Podocytopathies. Nat Rev Dis Primers. 2020; 6:68. 2: Motrapu M, et al., **Anders HJ*,** Anguiano L*. Drug Testing for Residual Progression of Diabetic Kidney Disease in Mice Beyond Therapy with Metformin, Ramipril, and Empagliflozin. J Am Soc Nephrol. 2020; 31:1729-1745. 3: Landini S, Mazzinghi B, Becherucci F, Allinovi M, Provenzano A, Palazzo V, Ravaglia F, Artuso R, Bosi E, Stagi S, Sansavini G, Guzzi F, Cirillo L, Vaglio A, Murer L, Peruzzi L, Pasini A, Materassi M, Roperto RM, **Anders HJ**, Rotondi M, Giglio SR, Romagnani P. Reverse Phenotyping after Whole-Exome Sequencing in Steroid-Resistant Nephrotic Syndrome. Clin J Am Soc Nephrol. 2020; 15:89-100. 4: Romoli S, et al., **Anders HJ***, Romagnani P*. CXCL12 blockade preferentially regenerates lost podocytes in cortical nephrons by targeting an intrinsic podocyte-progenitor feedback mechanism. Kidney Int. 2018; 94:1111-1126. 5: Romagnani P, et al., **Anders HJ**. Nextgeneration sequencing and functional analysis of patient urine renal progenitor-derived podocytes to unravel the diagnosis underlying refractory lupusnephritis. Nephrol Dial Transplant. 2016; 31:1541-1545. * equal contribution

7. SIGNATURE

Digital signatures or scanned signatures will be accepted. These signatures should be from the principal investigators listed in part 2. An official signature of the respective institutions is not necessary. A stamp of the Coordinator's institution (e.g. the relevant university institute or company) should be added.

Coordinator **Last Name: Romagnani** **First Name: Paola** **Institution: Meyer Children's Hospital**	**Stamp and Signature** **Date: 17.06.2021**

The project partners below have checked their regional/national regulations. They are informed about the content of this joined application.

Signature Partner 1:

Signature Partner 2:

Signature Partner 3:

The following template only has to be filled in by consortia that will perform a clinical study. Please delete if not needed.

Exploratory Clinical Studies - Template

APPLICANT/COORDINATING INVESTIGATOR	Name, address, telephone, fax, e-mail *In case of multiple applicants the principal investigator / coordinating investigator of the trial who will assume responsibility for conducting the clinical trial, should be listed first.*
TITLE OF STUDY	*Descriptive title identifying the study design, population, and interventions.*
CONDITION	*The medical condition being studied (e.g. lymphoma, M. Parkinson)*
OBJECTIVE(S)	*Which principal research questions are to be addressed? Specify clearly the primary hypotheses that determine sample size calculation.*
INTERVENTION(S)	*Brief description of the experimental and the control treatments or interventions, if applicable: dose and mode of application.* Experimental intervention: Control intervention: Duration of intervention per patient: Follow-up per patient:
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: Key exclusion criteria:
OUTCOME(S)	Primary efficacy endpoint: Key secondary endpoint(s): Assessment of safety:
STUDY TYPE	*e.g. randomized / non-randomized, type of masking (single, double, observer blind), type of controls (active / placebo), parallel group / cross-over*
STATISTICAL ANALYSIS	Efficacy: Description of the primary efficacy analysis and population: Safety: *Please describe the strategy for assessment of safety issues in the study. Which are relevant safety variables?* Secondary endpoints:
SAMPLE SIZE	To be assessed for eligibility (n = …) To be allocated to trial (n = …) To be analysed (n = …)
TRIAL DURATION	Time for preparation of the trial (months): Recruitment period (months): First patient in to last patient out (months):

	Time for data clearance and analysis (months): Duration of the entire trial (months):
PARTICIPATING CENTERS	To be involved (n): *if applicable; how many centres will be involved? Please also list the cities.*

MULTIDISCIPLINARY RESEARCH PROJECTS ON PERSONALISED MEDICINE – DEVELOPMENT OF CLINICAL SUPPORT TOOLS FOR PERSONALISED MEDICINE IMPLEMENTATION

PER-NEPH ERAPERMED2021-207

General Information

Keywords
Nephrotic syndrome, whole exome sequencing, podocytopathies, genetic testing, relapse

Project acronym
PER-NEPH

Project title (long title)
Implementation of personalised management in nephrotic syndrome

Project summary
Nephrotic syndrome in children and young adults is a frequent medical problem of very diverse pathophysiology and prognosis. Current diagnostic algorithms fail to avoid under- and overtreatment of patients with toxic drugs as defining the underlying cause is frequently difficult. We have developed a diagnostic algorithm of stratifying patients through advanced genetic testing, reverse phenotyping, and personalised disease models. This can double the current diagnostic rate in patients not responding to first line therapy and to predict disease relapse in those that progress to end stage kidney disease and have to undergo kidney transplant.
The aims of this project are to:
1. Implementation of this diagnostic algorithm in selected European sites by a) selecting patients for a personalised genetic diagnosis, b) whole exome sequencing and bioinformatic prioritization of potentially pathogenic variants, c) validating genotype-phenotype correlation for a personalised diagnosis, and d) personalising the assessment of variants of unknown significance by functional studies with patient urine-derived renal progenitors and 3D organ-on-a-chip disease models.
2. Personalising the assessment of non-genetic forms and of relapse after transplant by a) identifying patients negative to the genetic testing, b) assessing patients with proteinuria relapse after kidney transplant, c) personalising the detection of immunologic factors by using STED super-resolution microscopy and d) personalising the detection of circulatory permeability factors by using a 3D organ-on-a-chip model system.
3. Assessing the cost-effectiveness as well as clinical, ethical, and legal consequences of the proposed algorithm by a) a multicentre model-based cost-utility analysis of the proposed algorithm and by assessing the b) clinical, c) ethical, and d) legal consequences in close conjunction with the study participants and the respective patient organisations by standardised questionnaire tools.

Project duration (months)
36

Research Area 1:
Module 1A: Pre-clinical Research
Module 1B: Clinical Research

Research Area 2:
Module 2B: Data and ICT - Towards application in health care

Research Area 3:
Module 3A: Health Economic Research
Module 3B: Ethical, Legal and Social Aspects

Checklist for the coordinator

Verified
ok

Submission of the same research project to other calls:
No

precise
-

PER-NEPH ERAPERMED2021-207

Project Coordinator

Organisation legal name	Meyer Children's Hospital
Institute	Nephrology Unit
Street, No.	Viale Pieraccini 24
Zip code	50139
City	Florence
Country	Italy
Funding organisation	Tuscany Region, (TuscReg), Tuscany (Italy)
Gender	female
Year of birth	1970
Year of PhD	2001
Title	Prof.Dr.Med
Last name	Romagnani
First name	Paola
Phone number	+390555662562
eMail	paola.romagnani@meyer.it
Total requested budget for the coordinator (in EUR)“	170,000
Total project costs (in EUR) for the coordinator (in EUR)	266,312
Type of entity	Clinical / public health research sector

Project Partner (1/3)

Organisation legal name	University of Florence
Institute	Department of Clinical and Experimental Biomedical Sciences
Street, No.	Viale Pieraccini 6
Zip code	50139
City	Florence
Country	Italy
If other, please specify:	
Funding organisation	Tuscany Region, (TuscReg), Tuscany (Italy)
Gender	female
Year of birth	1974
Year of PhD or equivalent	2003
Title	Ph D
Last name	Lazzeri
First name	Elena
Phone number	+390552758165
eMail	elena.lazzeri@unifi.it
Total requested budget (in EUR)	130,000
Total project costs (in EUR)	227,190
Type of entity	Academia

Project Partner (2/3)

Organisation legal name	Bellvitge Biomedical Research Institute (IDIBELL)
Institute	Hospital of Bellvitge, Nephrology
Street, No.	Feixa LLarga s/n
Zip code	08907
City	L'Hospitalet de Llobregat
Country	Spain
If other, please specify:	
Funding organisation	Health Department – Generalitat de Catalunya, (DS-CAT), Catalonia (Spain)
Gender	male
Year of birth	1965
Year of PhD or equivalent	2000
Title	Professor Dr Medicine
Last name	Cruzado
First name	Josep Maria
Phone number	+34-93-2607604
eMail	jmcruzado@bellvitgehospital.cat
Total requested budget (in EUR)	192,120
Total project costs (in EUR)	239,920
Type of entity	Clinical / public health research sector

Project Partner (3/3)

Organisation legal name	University Hospital of the Ludwig-Maximilians University Munich (LMU Klinikum)
Institute	Division of Nephrology, Department of Internal Medicine IV
Street, No.	Ziemssenstr. 1
Zip code	80336
City	Muenchen
Country	Germany
If other, please specify:	
Funding organisation	Federal Ministry of Education and Research, (BMBF) / German Aerospace Center e.V. – Project Management Agency, (DLR), Germany
Gender	male
Year of birth	1967
Year of PhD or equivalent	2003
Title	Prof. Dr. med.
Last name	Anders
First name	Hans-Joachim
Phone number	+49-89-440053583
eMail	hjanders@med.uni-muenchen.de
Total requested budget (in EUR)	206,760
Total project costs (in EUR)	323,760
Type of entity	Academia

PER-NEPH **ERAPERMED2021-207**

Financial plan

	Name	Organisation legal name	Country	Requested funds (EUR)	Total funding volume (EUR)
Project coordinator	Paola Romagnani	Meyer Children's Hospital	Italy	170,000	266,312
Project partner	Elena Lazzeri	University of Florence	Italy	130,000	227,190
Project partner	Josep Maria Cruzado	Bellvitge Biomedical Research Institute (IDIBELL)	Spain	192,120	239,920
Project partner	Hans-Joachim Anders	University Hospital of the Ludwig-Maximilians University Munich (LMU Klinikum)	Germany	206,760	323,760
Overall				**698,880**	**1,057,182**

S.O.C. DI NEFROLOGIA
AOU MEYER
viale G. Pieraccini, 24 50139 Firenze

Supporting Letter

I support the submission of the transnational proposal "Implementation of personalised management in nephrotic syndrome", PER-NEPH to the **ERAPerMed Joint Transnational Call for Proposals (2021) for "Multidisciplinary Research Projects on Personalised Medicine – Development of Clinical Support Tools for Personalised Medicine Implementation**, providing the essential conditions for the implementation of the project, according to the work programme presented.

I am aware of the ERAPerMed JTC 2021 Call Text, the procedures and the national/regional rules and regulations, and confirm that the proposal fulfils our national/regional eligibility criteria in order to be eligible for the ERAPerMed JTC 2021.

Place, Date

Florence, 01/03/2021

Paola Romagnani

Name of the *(Lead Researcher[1])*

Signature of the *(Lead Researcher)*

UNIVERSITÀ
DEGLI STUDI
FIRENZE

DIPARTIMENTO DI
SCIENZE BIOMEDICHE
SPERIMENTALI E CLINICHE

Supporting Letter

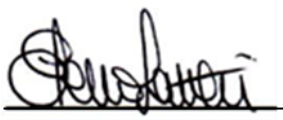
I support the submission of the transnational proposal "**Implementation of personalised management in nephrotic syndrome", PER-NEPH** to the **ERAPerMed Joint Transnational Call for Proposals (2021) for "Multidisciplinary Research Projects on Personalised Medicine – Development of Clinical Support Tools for Personalised Medicine Implementation**, providing the essential conditions for the implementation of the project, according to the work programme presented.

I am aware of the ERAPerMed JTC 2021 Call Text, the procedures and the national/regional rules and regulations, and confirm that the proposal fulfils our national/regional eligibility criteria in order to be eligible for the ERAPerMed JTC 2021.

Place, Date
Florence, 01/03/2021

Name of the *(Lead Researcher[1])*
Elena Lazzeri

Signature of the *(Lead Researcher)*



Prof. Elena Lazzeri
Viale G.Pieraccini, 6 – 50139 Firenze
tel +39 055 2758165 | e-mail: elena.lazzeri@unifi.it
P.IVA | Cod. Fis. 01279680480

LMU KLINIKUM
MEDIZINISCHE KLINIK UND POLIKLINIK IV
Lehrstuhl: Endokrinologie & Diabetologie
Direktor: Prof. Dr. med. Martin Reincke

Medizinische Klinik und Poliklinik IV, Direktion
Ziemssenstraße 1, 80336 München

Leitung / Direktor
Prof. Dr. med. Martin Reincke

Ihr Ansprechpartner
Nephrologisches Zentrum
Prof. Hans-Joachim Anders
Telefon +49 (0)89 4400-53583
Telefax +49 (0)89 4400-53379
hjanders@med.uni-muenchen.de

www.klinikum.uni-muenchen.de

ERAPerMed JTC 2021

Supporting Letter

I support the submission of the transnational proposal "*Implementation of personalised management in nephrotic syndrome* (PER-NEPH)" to the **ERAPerMed Joint Transnational Call for Proposals (2021) for "Multidisciplinary Research Projects on Personalised Medicine – Development of Clinical Support Tools for Personalised Medicine Implementation**, providing the essential conditions for the implementation of the project, according to the work programme presented.

I am aware of the ERAPerMed JTC 2021 Call Text, the procedures and the national/regional rules and regulations, and confirm that the proposal fulfils our national/regional eligibility criteria in order to be eligible for the ERAPerMed JTC 2021.

Munich, 26.02.2021

Name of the *(Lead Researcher[1])*
Prof. Dr. med. Hans-Joachim Anders

Signature of the *(Lead Researcher)*

Salut/ Bellvitge Hospital Universitari

Feixa Llarga, s/n
08907 L'Hospitalet de Llobregat
Tel. 932 607 500
bellvitgehospital.cat

Supporting Letter

I support the submission of the transnational proposal "**Implementation of Personalised Management in Nephrotic Syndrome** / ***PER-NEP***" to the **ERAPerMed Joint Transnational Call for Proposals (2021) for "Multidisciplinary Research Projects on Personalised Medicine – Development of Clinical Support Tools for Personalised Medicine Implementation**, providing the essential conditions for the implementation of the project, according to the work programme presented.
I am aware of the ERAPerMed JTC 2021 Call Text, the procedures and the national/regional rules and regulations, and confirm that the proposal fulfils our national/regional eligibility criteria in order to be eligible for the ERAPerMed JTC 2021.

Place, Date

L'Hospitalet de Llobregat, February 26th, 2021

Name of the *(Lead Researcher[1])*
JOSEP M CRUZADO

Signature of the *(Lead Researcher)*

JOSE MARIA CRUZADO GARRIT / num:08275410

Firmado digitalmente por JOSE MARIA CRUZADO GARRIT / num:08275410
Nombre de reconocimiento (DN): c=ES, st=BARCELONA, o=Col·legi Oficial de Metges de Barcelona / COMB / 0005, ou=COL·LEGIAT, title=NEFROLOGIA, sn=CRUZADO GARRIT, givenName=JOSE MARIA, serialNumber=40924429T, cn=JOSE MARIA CRUZADO GARRIT / num:08275410, email=jmcruzado@bellvitgehospital.cat
Fecha: 2021.02.26 09:26:43 +01'00'

To: Paola Romagnani, MD, PhD
Professor and Chair of Nephrology,
Department of Biomedical and Experimental Sciences 'Mario Serio'
Head of Pediatric Nephrology Unit, Meyer Children's Hospital University of Florence
Viale Pieraccini 6,
50139 Florence, Italy

Letter of support

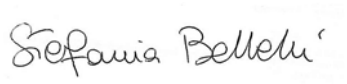
It is with great enthusiasm that I provide this letter to declare my availability for a collaboration with Prof. Paola Romagnani in her EraPerMed grant application entitled "Implementation of personalized management in nephrotic syndrome". My role in the project will be to collaborate on assessing the cost-effectiveness of the proposed algorithm for personalized diagnosis of nephrotic syndrome by a multicenter model-based cost-effectiveness analysis to assess prospectively the economic implications of performing a genetic testing by WES in patients with nephrotic syndrome.

The analysis will consider direct and indirect medical costs, and possibly direct non-medical costs and will include cost variations in the subsequent clinical surveillance and treatment. The same data will be also be collected for the evaluation of cost-effectiveness of cascade genetic testing in proband's relatives. The outcomes of the intervention will be measured as clinical effectiveness measures or quality-adjusted life-years (QALYs), using validated questionnaires. Results will be analysed in terms of incremental costs, consequences and, when appropriate, cost-effectiveness ratio (ICERc).

For this analysis, I will provide my personal expertise on this topic. I received a Degree in Statistics and Actuarial Sciences at the University of Florence, a PhD in Health Technology Assessment and Management (HTA and HTM) at University of Pisa and Scuola Superiore Sant'Anna, and a formal training in health economics with several training courses. I am actually involved in the mapping and monitoring of health equipment, evaluation of biomedical technologies and analysis of territorial pharmaceutical expenditure in the Piemonte Region, Italy. I have been involved as statistician and health economist in several national and international research projects including economic evaluations of health technologies.

Sincerely,

Torino, Italy, 12 June 2021



STEFANIA BELLELLI, ScD, PhD,
Researcher (t.i., D3), IRES Piemonte,
via Nizza 18, 10125, Torino, Italy

BRIGHAM AND
WOMEN'S HOSPITAL

HARVARD
MEDICAL SCHOOL

Department of Pathology
75 Francis Street
Boston, Massachusetts 02115

Tel: 617 732-7671, Fax: 617 264-5223
E-mail: aweins@bwh.harvard.edu

Astrid Weins, M.D., Ph.D.
Associate Pathologist
Assistant Professor of Pathology
Director, Renal Pathology Fellowship Program

Boston, June 11, 2021

Paola Romagnani, MD, PhD
Professor and Chair of Nephrology
Department of Biomedical and Experimental Sciences 'Mario Serio'
Head of Pediatric Nephrology Unit
Meyer Children's Hospital University of Florence
Viale Pieraccini 6
50139 Florence, Italy

LETTER OF SUPPORT

Dear Dr. Romagnani and Colleagues -

I am enthusiastic and honored to express my willingness to serve as your collaborator on your EraPerMed proposal entitled **"Implementation of personalized management in nephrotic syndrome"**.

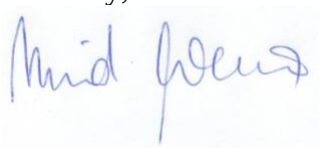
As you know, I am a Renal Pathologist at Brigham and Women's Hospital in Boston, MA, as well as an Assistant Professor of Pathology at Harvard Medical School. In my clinical practice, I evaluate approximately 800 renal biopsies per year, and have now over 10 years of experience in this field. I also have an active translational research program that focuses on mechanisms of podocyte injury and glomerular disease progression.

Recent research in my lab has shown that a high proportion of patients with primary podocytopathies have anti-nephrin antibodies that could be detected in the biopsies as well as in the sera of these patients – our work was presented at the ASN Renal Week 2020 and has been published as a non-peer-reviewed preprint on MedRxiv (Watts AJB et al. **doi:** https://doi.org/10.1101/2021.02.26.21251569). In my lab, we have started to study patients with primary FSGS (focal and segmental glomerulosclerosis) who progressed to ESKD and those who received a kidney transplant, using a stringent definition to define primary FSGS in the native kidney as well as in the allograft. Our preliminary results on the potential role of anti-nephrin antibodies in progressive podocytopathies and in those patients who develop recurrent proteinuria with morphologic findings mirroring the patient's primary podocytopathy ("recurrent FSGS") are very encouraging.

Historically, studying FSGS has been hampered by a very unfortunate contamination of the studied cohorts with secondary FSGS and thus, dilution, non-reproducibility of results and lack of clinically consequential data. I believe it would be of great benefit to your study to identify those patients that are positive for the presence of circulating anti-nephrin antibodies during active nephrotic syndrome, and I herewith agree to perform these studies in my laboratory based on the ELISA and IP methodologies we have validated and implemented as described in the manuscript above.

I very much look forward to collaborating with you on this research proposal. Your project is timely and clinically very relevant.

Sincerely,



Astrid Weins, MD, PhD
HMS Assistant Professor of Pathology
BWH Associate Pathologist