KDIGO Controversies Conference on Genetics in CKD

- Public Review Comments -

As of January 4, 2021
Industry comments are highlighted in blue

Baris Afsar - Suleyman Demirel University
This conference is timely. It will certainly be helpful for the physicians and opens availability for personalised care. I think it would be helpful also to include genetic-epigenetic interactions for the pathogenesis and treatment of kidney diseases.

Anthony Bleyer - Wake Forest School of Medicine
1) I would like to see a little more from the patient perspective. I have several patients who would be happy to present their experience if this would be beneficial or helpful.

2) How should the gene panels from the different commercial vendors be compared or used? How does a nephrologist know which company to pick? KDIGO cannot make specific recommendations, but from a practical standpoint, it is quite difficult for the ordinary nephrologist to decide how to go about testing and what company to use? Perhaps we could discuss attributes that make a gene panel superior: eg number of genes tested, direct cost to the patient.

3) What about the reporting of variants of undetermined significance and how the primary nephrologist should interpret these? On the one hand, we do not want to overdiagnose a disease. On the other hand, there are likely many new mutations that cause a disease?

4) Do patients have a right to be offered genetic testing for likely genetic conditions? Many patients are not given this option.

Olivier Devuyst - University of Zurich
P1: Include arguments for the strong genetic basis of CKD (heritability, ethnicity, animal studies…)?

P1: Identification of the genetic basis of rare diseases has led to new classification and ontology of kidney disorders; go beyond clinically-based classifications.

P2: The conference overview could refer to the series of KDIGO conferences which elaborated on genetic findings and analyses in a set of specific rare diseases.

P4 (Group 1): 1. Wonder if the discussion should not include "rare" vs. "common" disorders; mention germline vs. somatic mutations; shift of boundaries in "pediatric" vs. "adult" disorders; include clear evidence for modifier effects.

P4, point 2: Discuss the importance of functional assays (e.g. PKD database – lacking such robust assays); how to report VUS; standards for causality, number of mutations/families for a new disease gene; importance (and limitations) of public databases.

P4, point 4: economy of genetic testing; consent of children; criteria of quality for genetic testing, academic vs. private; uniformization of testing: discussion of common panels, revision of such panels, WES vs. panels vs. MLPA; remaining technical difficulties/limitations to testing

P4, point 5: Genetic heterogeneity and nomenclature – clinical entity vs. genetic analysis (e.g. ADPKD, Dent disease, quid of unsolved cases, ADTKD-UMOD would be a better example than ADTKD-MUC1 due to the difficulty of testing for MUC1….

P5, point 2: tubulopathies could be included – heritability studies, disease entities matching tubular functions. P7: "Genomic nephrology" or "nephrogenetics"? Discuss storage and potential for reusing WES/WGS data over lifetime; provisions of the informed consent; cost and uniformity of genetic testing – guidelines from ISN? Promote cost-effective mini-panels?

P8, point 1: Should you start with genomic information (now in b) and then go into non-genomic parameters (now in a)?

P8, point 2: Transplant - discuss genetic info from donors vs. recipient; consent, ethics P8, point 4a: Importance of EMRs for multi-systemic, complex phenotype identification; phenotype-based guidance.

P9: Clinical trials – importance of genetic makeup in populations; ensure diversity; integrate epigenetics, aging aspects

Kevin Fowler - The Voice of Patient, Inc.
I have listed questions that I am recommending to included in the breakout groups.

Breakout Group 1:
1)What are the barriers to genetic testing: psychological, insurance discrimination, cost, lack of treatments for genetic kidney disease, etc.

2)What is being done to remove barriers to genetic testing?

3) Are patients with genetic kidney diseases without treatments being offered the opportunity to participate in clinical trials?

4) For patients with genetic kidney diseases without treatments, how are they being taught to advocate for research funding and treatments?

Breakout Group 3:
To reduce the time to diagnosis and treatment, how do patients find nephrologists that are trained to diagnose their genetic condition and receive proper treatment?

Breakout Group 4:
The PKD Consortium is an effective partnership between the PKD Foundation and the Critical Path Institute. Why aren't these success stories being shared with other fledgling genetic kidney disease groups?

Oliver Gross - University Medicine Goettingen, Goettingen, Germany
Dear KDIGO Genetics in CKD Team,

Thank you very much for this great effort to bring this together.

May I suggest an additional Point to your "Breakout Group 1: Monogenic Kidney Diseases" or maybe it even fits better to "Breakout Group 2: Complex Kidney Diseases" There is a strong need to discuss the topic "FSGS and Alport-variants". One third of all Alport patients are misdiagnosed as FSGS (Groopman, NEJM 2019), treated with immunosuppressants, receive a wrong conselling regarding recurrance after kidney transplant etc.

The "Alport community" addresses this as a very important unmet medical need: the KDIGO Genetics in CKD conference would be the ideal place to discuss common elements and give recommendations. According to the NEJM paper by Groopman et al. in 2019, In our guidelines for Alport (Kashtan&Gross, Ped Nephrol 2020), weHere, we "emphasize that a significant percentage of patients with the histological changes of focal segmental glomerulosclerosis (FSGS) are found to have pathologic Collagen IV gene variants and therefore should be diagnosed with Alport syndrome, in order to avoid ineffective and potentially harmful immunosuppressive therapy." The Alport community has no "official KDIGO platform" to discuss this topic, so your KDIGO Genetics in CKD Conference would be the ideal place. I am aware Andre Weinstock from the Alport Syndrome Foundation might take part at you conference, which is a perfect match (he has Alport's). Maybe, a clinician Alport expert such as Clifford Kashtan, Michelle Rheault (Minneapolis), James F. Simon (Cleveland) or myself would also be good candidates to contribute to your conference.

Warm wishes,
Oliver Gross

Julia Hoefele - Institute of Human Genetics, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany
Dear Sir or Madam,

It is a great pleasure for us to provide you with feedback on the Scope of Work for the Genetics in CKD Controversies Conference. We would be delighted if some of our comments below could be discussed on this conference.

Kind regards,
Julia Hoefele (on behalf of the nephrogenetic working group members Korbinian M. Riedhammer, Matthias C. Braunisch, and Jasmina Comic)

Breakout Group 1:
1) Guidelines for sequence variant interpretation. The widely used ACMG guideline for the interpretation of sequence variants (Richards et al., 2015) have been refined (stricter interpretation) over the recent years (see, for example, Abou Tayoun et al., 2018, and the ACGS guidelines 2019/2020, Ellard et al., 2019/2020). We therefore recommend to consider updates to the ACMG criteria in evaluation of variants of monogenic kidney diseases. Furthermore, there are current ACMG guidelines for CNV interpretation (Riggs et al., 2020), which also should be used.

2) What variants should be reported in the genetic report? --> Reporting of VUS There should be a discussion in the breakout group on reporting of variants of uncertain significance (VUS). Recent guidelines (ACGS; Ellard et al., 2020) proposed strict criteria when VUS should be reported. Basically, VUS should only be reported if further testing can be undertaken to re-classify the variant as likely pathogenic (testing of parents, biochemical, functional tests). Other VUS can be divided in several categories of evidence level according to ACMG criteria ("hot", "warm", "tepid", "cool", "cold", "ice cold") and should only be reported in exceptional cases following a multidisciplinary discussion. The breakout group should discuss this approach. Reporting of VUS without the chance of re-classifying the variant results in uncertainty (both in the referring clinician and the patient) as to what consequences genetic reports have. VUS are likely to be found in comprehensive sequencing (like exome and genome sequencing), as can be seen in the ExAC dataset (exomes of 60,706 humans): About 50% of identified variants were novel (singletons; see Lek et al., 2016).

3) Recommendation of re-analysis of exome/genome data after a specific time (1-2 years)? In one study of 500 exomes of a commercial lab, 23% of positive findings where within genes that had been characterized as disease-associated within the past two years. A novel gene finding was identified in about 8% of cases (Farwell et al., 2015). Hence, we think it is important to discuss a regular, systematic re-analysis of unsolved genome-wide data (exome/genome sequencing) in the breakout group.

4) Should it be obligate that variants must be submitted to worldwide databases like ClinVar, LOVD? We would like to propose that researchers submit genetic variants not only to disease specific and limited access databases but to international and publicly available

databases, like ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and LOVD (https://www.lovd.nl).

Breakout Group 3:
1) Should there be implemented a worldwide standard genetic diagnostic setting for patients with kidney diseases? Finally, due to the emerging availability of genetic testing and information we would like to emphasize a discussion on a worldwide ethical standard on the access to molecular diagnostics, interpretation and treatment for patients with hereditary kidney disorders as well as the implications of this sensitive information for individuals with a hereditary kidney disease (and their families) (Martin et al., 2020).

References: Abou Tayoun, A.N., Pesaran, T., Distefano, M.T., Oza, A., Rehm, H.L., Biesecker, L.G., Harrison, S.M., and Clingen Sequence Variant Interpretation Working, G. (2018). Recommendations for interpreting the loss of function PVS1 ACMG/AMP variant criterion. Hum Mutat 39, 1517-1524. Ellard, Baple, Callaway, Berry, Forrester, Turnbull, Owens, Eccles, Abbs, Scott, Deans, Lester, Campbell, Newman, Ramsden, and Mcmullan (2020). ACGS Best Practice Guidelines for Variant Classification in Rare Disease 2020. Ellard, S., Baple, E., Berry, I., Forrester, N., Turnbull, C., Owens, M., Eccles, D., Abbs, S., Scott, R., Deans, Z., Lester, T., Campbell, J., Newman, W., and Mcmullan, D. (2019). ACGS Best Practice Guidelines for Variant Classification 2019. Farwell, K.D., Shahmirzadi, L., El-Khechen, D., Powis, Z., Chao, E.C., Tippin Davis, B., Baxter, R.M., Zeng, W., Mroske, C., Parra, M.C., Gandomi, S.K., Lu, I., Li, X., Lu, H., Lu, H.M., Salvador, D, Ruble, D., Lao, M., Fischbach, S., Wen, J., Lee, S., Elliott, A., Dunlop, C.L., Tang, S. (2015). Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. Genet Med 17, 578-586. Lek, M., Karczewski, K.J., Minikel, E.V., Samocha, K.E., Banks, E., Fennell, T., O'Donnell-Luria, A.H., Ware, J.S., Hill, A.J., Cummings, B.B., Tukiainen, T., Birnbaum, D.P., Kosmicki, J.A., Duncan, L.E., Estrada, K., Zhao, F., Zou, J., Pierce-Hoffman, E., Berghout, J., Cooper, D.N., Deflaux, N., DePristo, M., Do, R., Flannick, J., Fromer, M., Gauthier, L., Goldstein, J., Gupta, N., Howrigan, D., Kiezun, A., Kurki, M.I., Moonshine, A.L., Natarajan, P., Orozco, L., Peloso, G.M., Poplin, R., Rivas, M.A., Ruano-Rubio, V., Rose, S.A., Ruderfer, D.M., Shakir, K., Stenson, P.D., Stevens, C., Thomas, B.P., Tiao, G., Tusie-Luna, M.T., Weisburd, B., Won, H.H., Yu, D., Altshuler, D.M., Ardissino, D., Boehnke, M., Danesh, J., Donnelly, S., Elosua, R., Florez, J.C., Gabriel, S.B., Getz, G., Glatt, S.J., Hultman, C.M., Kathiresan, S., Laakso, M., McCarroll, S., McCarthy, M.I., McGovern, D., McPherson, R., Neale, B.M., Palotie, A., Purcell, S.M., Saleheen, D., Scharf, J.M., Sklar, P., Sullivan, P.F., Tuomilehto, J., Tsuang, M.T., Watkins, H.C., Wilson, J.G., Daly, M.J., MacArthur, D.G.; Exome Aggregation Consortium (2016). Analysis of protein-coding genetic variation in 60,706 humans. Nature 536, 285-291. Martin, D.E., Harris, D.C.H., Jha, V., Segantini, L., Demme, R.A., Le, T.H., Mccann, L., Sands, J.M., Vong, G., Wolpe, P.R., Fontana, M., London, G.M., Vanderhaegen, B., Vanholder, R., and Nephrology, A.-E.-E.-I.J.W.G.O.E.I.I. (2020). Ethical challenges in nephrology: a call for action. Nat Rev Nephrol 16, 603-613. Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W.W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., and Rehm, H.L. (2015). 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 17, 405-424. Riggs, E.R., Andersen, E.F., Cherry, A.M., Kantarci, S., Kearney, H.,

Patel, A., Raca, G., Ritter, D.I., South, S.T., Thorland, E.C, Pineda-Alvarez, D., Aradhya, S., Martin, C.L. (2020). Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Genet Med 22, 245-257.

Fan Fan Hou - Nanfang Hospital, Southern Medical University; National Clinical Research Center for Kidney Disease

The scope of work is comprehensive and includes all clinically concerned issues regarding genetics in CKD. A few comments as follows:

1) To assess genetic contributions to complex kidney diseases, RNA sequence and non-coding RNA, in addition to DNA (GWAS), may also be discussed.

2) What ethical or guiding criteria should be developed to decide when pregnant patients with hereditary kidney disease should be referred to prenatal diagnosis of the hereditary kidney disease?

Craig Langman - Lurie Children's Hospital of Chicago and Feinberg School of Medicine

Given that there are now many programs for free genetic testing of CKD and associated conditions (stones for example), why shouldn't all patients with CKD and or stones have this done? What are the core competencies that need to be part of training in fellowship programs about genetics.

Matthew Lanktree - McMaster University

Genetic tests are available for many kidney diseases and clinical clues increase the probability of identifying a rare pathogenic variant. On one hand a genetic test can seal a diagnosis, but this may not meaningfully impact care. Adult patients without family history are particularly challenging as diagnostic yield is going to be drastically lower, but the ramifications of a positive test are much larger.

The primary challenges in clinical genetic testing in Nephrology are:
1) selecting the right patient for the genetic test, not just the patient most likely to have a variant but whose management will be altered by the test;

2) selecting the most appropriate test, lab provider, physician and genetic counsellor with access and expense in mind;

3) correctly ascribing the degree of risk to an identified variant, as incomplete penetrance and variable expressivity are common and confirmation bias can make it easy to incorrectly assign pathogenicity;

4) educating patients about ramifications of genetic testing particularly as it varies from country to country and

5) the cost associated with genetic testing and preponderance or research in European populations that may further exacerbate disparities of health outcomes.

While a unified answer to these questions across all kidney diseases would be ideal, I'm afraid the rationale varies from disease to disease, and recommendations may need to be target to specific etiologies (ie. ADPKD vs. Type IV collagen nephropathy).

I would be absolutely thrilled to be involved in the discussions of the KDIGO controversies conference if provided the opportunity.

Trudy McKanna – Natera

My two questions were: - are pharmacogenomics being covered? - is there any discussion on community-based participatory research? Trudy

Alberto Ortiz - Fundación Jiménez Díaz

In order to assign a diagnosis of CKD of unknown origin, what studies should be performed to exclude genetic kidney disease? Mind that the proposed nomenclature would be:

1. CKD of unknown origin, when the tests necessary to exclude genetic kidney disease have been performed and no cause identified and no other etiological diagnosis can be ascribed

2. CKD without diagnostic workup. CKD for which no complete diagnostic workup was completed, for example, because genetic kidney disease was not excluded The absence of a genetic workup may be justified in clinical grounds The general idea would be to define an etiological workup with etiological diagnostic criteria that allows a more reliable etiological diagnosis. The full etiological workup may not be indicated for all CKD patients. However, if not completed, we should be honest and diagnose of "CKD without complete diagnostic workup" rather than using "hypertensive nephropathy" or "unknown cause". This would be a stepping stone towards precision nephrology.

Some of these ideas developed in Carriazo S, Vanessa Perez-Gomez M, Ortiz A. Hypertensive nephropathy: a major roadblock hindering the advance of precision nephrology. Clin Kidney J. 2020 Sep 2;13(4):504-509. doi: 10.1093/ckj/sfaa162.

Ronald Perrone – Tufts Medical Center

Congratulations on putting together a very exciting conference. One item missing from the agenda, which likely will not be solved at the conference, is the implementation of genetics into ROUTINE nephrology practice, not for those who are experts running labs. Perhaps this will be identified as a clinical/research need. -which form of genetic testing should be done-WES, vs NGS using kidney-specific panels? specific targeted Sanger sequencing as is

frequently done for ADPKD, other? -who should do the testing? commercial vs research labs? frequently research labs not CLIA-certified. -how will this be paid for? resistance of insurers to cover costs -who is responsible for calling variants of unknown significance over the long term? I believe that this responsibility lies with those entities performing the test but should be a mandate for these entities to keep evaluating these VUS and communicate back to the ordering provider. -is there value to establishing centers of excellence/genetic nephrology clinics which can collaborate with the primary providers, both in terms of consultation regarding which testing, who does it, how paid for, and communication of results? Use of telemedicine to facilitate these interactions would greatly facilitate availability of genetic expertise to the practicing nephrologist without geographic/travel constraints, even when coronavirus is vanquished. thanks for considering these comments. Ron Perrone

Deepak Sharma- Ketav Kalp Healthcare & Research Private Limited
A well-researched and considered scope of work.

Michael Spigler - American Kidney Fund
The American Kidney Fund (AKF) is very excited to see this program coming together and would be honored to participate if invited. We were so glad to have John Davis represent KDIGO at our Unknown Causes of Kidney Disease Summit on December 1. This scope of work looks very intriguing and comprehensive.

As AKF serves one of the largest contingents of underserved kidney patients in the country, we are very pleased to see Question 7 in Breakout Group 3 focus on equitable access. As discussed in several breakout groups at our Summit, the divide between different groups can be immense in this area, and has been exacerbated by COVID-19.

Albertien M. van Eerde - Expert Centre Hereditary and Congenital Nephrologic and Urologic Disorders, UMC Utrecht, The Netherlands
Dear Colleagues,

Congratulations on and good luck with organizing this meeting. I am very enthusiastic about the scope of this Controversies conference, I hope I can contribute to the actual conference in March. Many (if not all) of my professional roles are entwined with the topics of the conference. Examples would be:

1) my coordinatorship and clinical practice of and in our ERKNET accredited expert center for genetic kidney disease, with not only multidisciplinary clinics with nephrologists and geneticists, but also genetics-paediatric nephrology and nephrology-obstetrics to cover the whole cycle of life, including extensive experience in counseling reproductive options, and weekly case discussions amongst others in the nephropathology meeting.

2) my scientific interest leading the nephrogenetic group in the UMC Utrecht with as main two foci Genetic causes of CKD and Reproductive nephrology, and a recently started pilot project with our Health Technology Assessment group

3) my authorship of the guideline for the Dutch Federation for Nephrology: Genetics for Nephrologists (2018; available online, in Dutch; https://www.nefro.nl/sites/www.nefro.nl/files/richlijnen/Handreiking%20genetische%20diagnostiek%20bij%20nierziekten%2C%202018.pdf); with recommendations on all aspects of diagnostics in and care for patients with (potentially) genetic renal disease.

4) My efforts to educate colleagues in practical nephrogenetics on all levels: I teach Nephrogenetics as a regular topic often together with a (pediatric) nephrologist, both in the national curricula for (ped) nephrologists in training and clinical geneticists in training. But I also co-organized a European CME on "how to become your local nephrogeneticist" (joint venture between ERA-EDTA several working groups and ERKNET). Also from the Expert center we have recently started an online multidisciplinary case discussion meeting with our experts (nephrologists, ped nephrologists, pathologist, obstetrician, clinical geneticist, laboratory genetic specialist) aimed to offer an accessible platform for case discussion to nephrologists that don't have the level of expertise available in their own center. Through "all these eyes", I went through the Scope of Work document and would like to mention a few things that might be of help in preparing, I would be happy to elaborate or discuss if you would want.

Contentwise: ---------- In general , throughout the conference it can be helpful to clearly make a distinction between the two main reasons for genetic testing : 1) to establish a diagnosis, in unknown, but also in atypical 'known' etc 2) for reproductive options/family advice including related donation (and 3) also in the clinical cases where there's not much doubt about the diagnosis nor need in the family, we will only identify the outliers if we do the testing, but obviously in that case scarcity arguments are also at play).

Page 4 Breakout group 1.1 : For the estimates of proportion of monogenic disease, it might be good to also have an eye out for other subclasses than the subclass CKD /renal failure (like nephrotic syndrome tubulopathies etc) this as the definition of specific diagnoses (and therefore also CKD of unknown origin) varies widely, and it is important colleagues can make an educated estimate for their own population/patient.

Breakout group 1.2: I am a bit puzzled by the wording here: "How can nephrologists ensure…" This implicates it should be the standard that nephrologists are leading in quality control of genetic testing for kidney diseases, where in many countries genetics services and labs are in place in order to guide the process. The ideal situation is some/any kind of multidisciplinary set-up with a lot of cross talk between specialties, and maybe words along those lines would better guide this part of the session.

Breakout group 1.3 And to add; can we define different categories of "actionable" (with one of them being "having additional reproductive options/information")

Breakout group 1.4 -to add; what is kidney failure of unknown etiology? This is a rhetoric question (also see 1.1), but in our Dutch guideline it led to a broader indication for genetic testing: kidney failure where one can't be sure the clinical diagnosis is correct, and it led to the advice to regularly review family history and primary kidney disease diagnosis, esp. in reproductive age. -also, to add, in which cases where testing might be indicated, mainstreaming is not the best way to go and referral to a clinical geneticist is indicated. In the Dutch situation for instance presymptomatic genetic testing is a prerogative of geneticists, but also in case of a) complex family dynamics (for instance monozygotic twins and one wants to know , the other doesn't or other situations where by testing person A , person B might also unknowingly or unwantingly get a diagnosis) or b) large genepanels (define nr of genes? specify type of content of panel?) and open WES, referral to a geneticist is necessary.

Page 7 Breakout group 3.1: Here the wording likely should be nephrologists instead of clinicians (as they might be clinical geneticists or nephrologists). In the Dutch guideline we drew up a list of "things you need to know and do" in pretest counseling and posttest returning of results. Clinical knowledge general: -It might be worthwhile to have a discussion on the definition of mainstreaming. I have come across colleagues who think it means they should know and do all from consenting to variant filtering and interpretation and counseling reproductive options etc etc. In this perspective it is daunting, and only few experts will master (also see 1.2). Yet, if we define mainstreaming in nephrology as: Next to a clinical geneticist/counselor, who did the testing to begin with, and will not stop doing that (so referral always possible), nephrologists are handed a toolbox including on who to test, how to do pretest counseling, how to read a result (and consult a specialist when in doubt) and do the first return of results before referral for counseling, it becomes much less daunting, and more generally feasible. In countries where genetics services aren't properly in place the KDIGO document might actually be an incentive to get it in place. -it might be helpful to explore/ list the differential diagnosis of a negative result (also in terms of ways in which there might still be a monogenic cause), so our colleagues are helped in their clinical reasoning/ assessing whether they need to discuss the patient in a multidisciplinary meeting/refer etc. In this respect; it would likely be helpful if we also give some clues as to when and when not to advise screening in relatives (BP and proteinuria; as they are actionable), even if no cause is proven. -it would maybe benefit our patients if we indicate/list in a byline other categories of genetics referral reasons: potentially hereditary cancersyndromes/ multiple miscarriages / familial aneurysms/ unexplained cardiomyopathy etc etc

Breakout group 3.4: Just happy to share that as of this week we have a nephrology resident who will do an internship in nephrogenetics in our expert center. Hopefully more will follow.

Breakout group 3.5: Few things: It makes things more clear if a distinction is made between a) obstetric preconception advice: risks for mother and child and planning of follow-up in pregnancy given the CKD in de mother and b) the need for genetic diagnostics and /or counseling, the latter one concerns both sexes (!). Along these lines; even when there is no

monogenic diagnosis, but for instance CAKUT in the prospective father, in the Netherlands it would be an indication for extensive ultrasound screening in pregnancy.

Breakout group 3.7: In this session one might also explore : What are the different ways in which patients are legally protected against DNA discrimination (higher insurance/mortgage fees or none possible etc), and what can we learn. -suggestion for reading on access inequality for PGT for renal disease in the US: PMID: 32895299

From a global perspective: one might also explore when nephrogenetics testing should be made part of standard care. I have been in discussions on research projects for evaluating the prevalence of monogenic disease in sub-Saharan African countries. Questions arose: even if tests are cheaper and cheaper, the amount of money involved in one test (even if we were to pay) might still pay for i.e. a nurse for a good part of the year; would that be a moral problem? Especially in areas where transplant let alone reproductive options or personalized treatment are not available, and even if people know they are at risk for offspring with renal disease, they will still have many children because they need support into old age. Likely there is some kind of tipping point; a standard of health care that needs to be in place before nephrogenetics should be implemented in standard care at all.

Page 8 Breakout group 4 -Does carrying a CAKUT related pathogenic mutation, with no apparent phenotype at age x (18?) pose a risk of CKD later in life, and if yes, is it enough to advise yearly follow-up?

Minor suggestions/semantics: ---------- Page 1 Sentence before last: Yet in other kidney diseases… Page 2 Line 4: Genetic findings in monogenic kidney diseasesare… Line 17: ….kidney biopsy results, when available……..and other sources of -omic data including findings resulting from association studies Page 4: Breakout group 1.2: (e.g. PKD-database / LOVD Alport) Breakout group 1.4: (e.g familial kidney disease, related living donor kidney transplantation, extra-renal features) Breakout group 1.5: (ClinGen, or curating HGMD, and others) Page 5 Breakout group 2.3: Which common risk factors Page 10 Not completely unbiased ;) papers to maybe consider as references PMID: 32855195, PMID: 27633871

Xiangling Wang - Cleveland Clinic

I am truly excited about this conference and looking forward to the statement! Given the limited resource of renal genetics professionals and centers, I would suggest the conference include the discussion of renal genetics center of excellence and utilization of telemedicine in the " Breakout group 3-Achieving Implementation in Clinical Medicine". Thank you!