Chronic Kidney Disease

Genetic Testing Recommendations

PROVINCIAL GENETICS PROGRAM

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Introduction

Ontario Health is building a comprehensive and integrated system for clinical genetic services across the province. Through collaboration with health system partners, the Provincial Genetics Program (PGP) provides evidence-based guidance for genetic diagnostic testing and counselling services in key areas. The PGP and the Provincial Genetics Advisory Committee (PGAC) identified kidney genetics as a priority domain for development in Ontario, resulting in the formation of the Renal Genetics Expert Group. Following an initial priority-setting exercise completed by the members of the Expert Group, limited availability of genetics tests was identified as the current greatest challenge in the delivery of kidney genetic testing in Ontario.

The recommendations in this report were initially developed through a review of the literature and refined and approved by the Renal Genetics Expert Group. In collaboration with health care professionals, laboratory scientists, administrators, and patient and care partners, the Expert Group established genetic testing recommendations for individuals with genetic kidney disease in Ontario.

Please note that data about prevalence, detection rate of molecular testing, penetrance, and age of diagnosis represents the best data available in the literature, which remains limited for some of the conditions presented.

Guidance Document Scope

This document offers recommendations related to the eligibility for genetic assessment and testing for genetic kidney disease, with a focus on the following:

- Eligibility criteria for genetic testing in affected individuals
- Clinical implementation considerations
- Evidence-based multigene panels and descriptions

The intended audience for this document includes clinical and molecular geneticists, genetic counsellors, adult and pediatric nephrologists, urologists, laboratory specialists, and other non-genetics clinicians, who provide care to patients and families with known or suspected genetic kidney disease. This document does not address monogenic diabetes, aldosteronism and other primary endocrine disorders, or kidney cancers as they may be covered by the work of other PGP Expert Groups. Polygenic risk scores and risk alleles, except for the *APOL1* risk alleles, are not included in this guidance document, as they have not been clinically validated. In addition, functional testing is outside the scope of this document.

Equity Considerations

Estimated Glomerular Filtration Rate Calculations

The PGP aims to develop equity-informed recommendations that recognize the impact that health policy can have on health outcomes in individuals, particularly in underserved or underrepresented populations. In this document, where possible, the use of estimated glomerular filtration rate (eGFR) and stages of kidney disease as eligibility defining characteristics was limited in response to emerging

evidence and expert opinion that challenge the use of 'race' as a biological construct in race-based calculations and the impact of such measures on access to timely care[1]. These calculations have been shown to misdiagnose and delay referrals to specialty care and kidney transplantation in patients with chronic kidney disease (CKD), thereby disproportionally affecting certain populations[2–4]. The eligibility recommendations for genetic testing, therefore, rely on a comprehensive assessment of kidney function rather than race-based risk assessment. Ontario Health - Ontario Renal Network (ORN) has validated the use of the CKD Epidemiology Collaboration (CKD-EPI) 2021 race-free equation and implementation is ongoing. In addition, the CKD-EPI 2021 equation has been endorsed by the Canadian Society of Nephrology as well as the National Kidney Foundation and American Society of Nephrology[5,6]. To support discussions about ending race-correction in kidney care and the implementation of the CKD-EPI 2021 equation, Ontario Health has developed resources to support the transition:

- **Patient Fact Sheet:** A New Race-Free Calculation for Measuring Kidney Function (also in French)
- **Clinician Resource:** A New Race-Free Equation for Estimating Glomerular Filtration Rate

Of note, the recommendations for clinicians state that the previous and current equations are only estimates and that "treatment decisions related to CKD care and diagnosis should focus on multiple measurements including albuminuria, serial changes in eGFR and of course, on clinical judgment".

APOL1 Testing

In alignment with the National Kidney Foundation and the American Society of Nephrology[7], *APOL1* testing should be included as part of a multigene panel offered to all patients, regardless of race or ethnicity. This approach accounts for inaccuracies of self-reported race and the limitations of using social constructs, such as race and ethnicity, to infer biological classifications like genetic ancestry[7,8]. To ensure inclusivity and equity, we recommend incorporating *APOL1* testing in the proteinuric and comprehensive kidney disease panels.

Background

The Kidney Disease Improving Global Outcomes (KDIGO) definition of CKD is kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, that can lead to decreased GFR, manifested by either pathological abnormalities or markers of kidney damage including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests[9]. In Canada, there are at least 4 million people with CKD, consistent with an estimated global prevalence of 11–13%[10–12]. A 2020 Canadian study found that over 50,000 individuals in Canada have kidney failure, with the highest prevalence in Ontario[13]. To date, hundreds of monogenic causes of CKD have been identified[14–17]. Genetic causes of kidney disease account for 10–20% of CKD cases in adults[17,18], with a higher prevalence in children and in individuals with additional risk factors[15,19,20]. Some examples are those with a family history of CKD, extra-renal features or specific subtypes of CKD, which are more likely to have a genetic form of kidney disease[14,15,21,22]. Recent evidence demonstrates that instituting a workflow, based on well-defined clinical criteria for genetic testing, leads to high diagnostic rates following genetic assessment [23–26].

Data suggests that confirming a diagnosis of genetic kidney disease leads to a meaningful change in treatment and management for 90% of cases, including changes in treatment plans, referrals to genetic counselling or genetic testing for relatives, and informing discussions around family planning[18]. Despite these benefits, genetic testing is not yet a routine part of the diagnostic pathway for CKD and too often performed late in the process[19,27]. Along with enhancing clinical utility, genetic and genomic testing can be cost-effective, especially when done early in the diagnostic pathway[25,28,29]. The cost of CKD to the Canadian healthcare system remains high, estimated at $40 billion annually, much of which is driven by the progression to kidney failure[11,30]. Early detection is therefore important, considering that patients with genetic kidney disease are at a higher risk of progression to kidney failure compared to those with non-genetic forms of CKD[31].

Confirming a genetic diagnosis can have added benefits beyond the index patient, by facilitating early identification of at-risk relatives thereby reducing the diagnostic odyssey for subsequent family members[19]. Cascade testing can support family planning, reduce costs, reduce time to diagnosis, negate the need for unnecessary or invasive diagnostic procedures, and impact treatment and management decisions for at-risk family members[16,21,28].

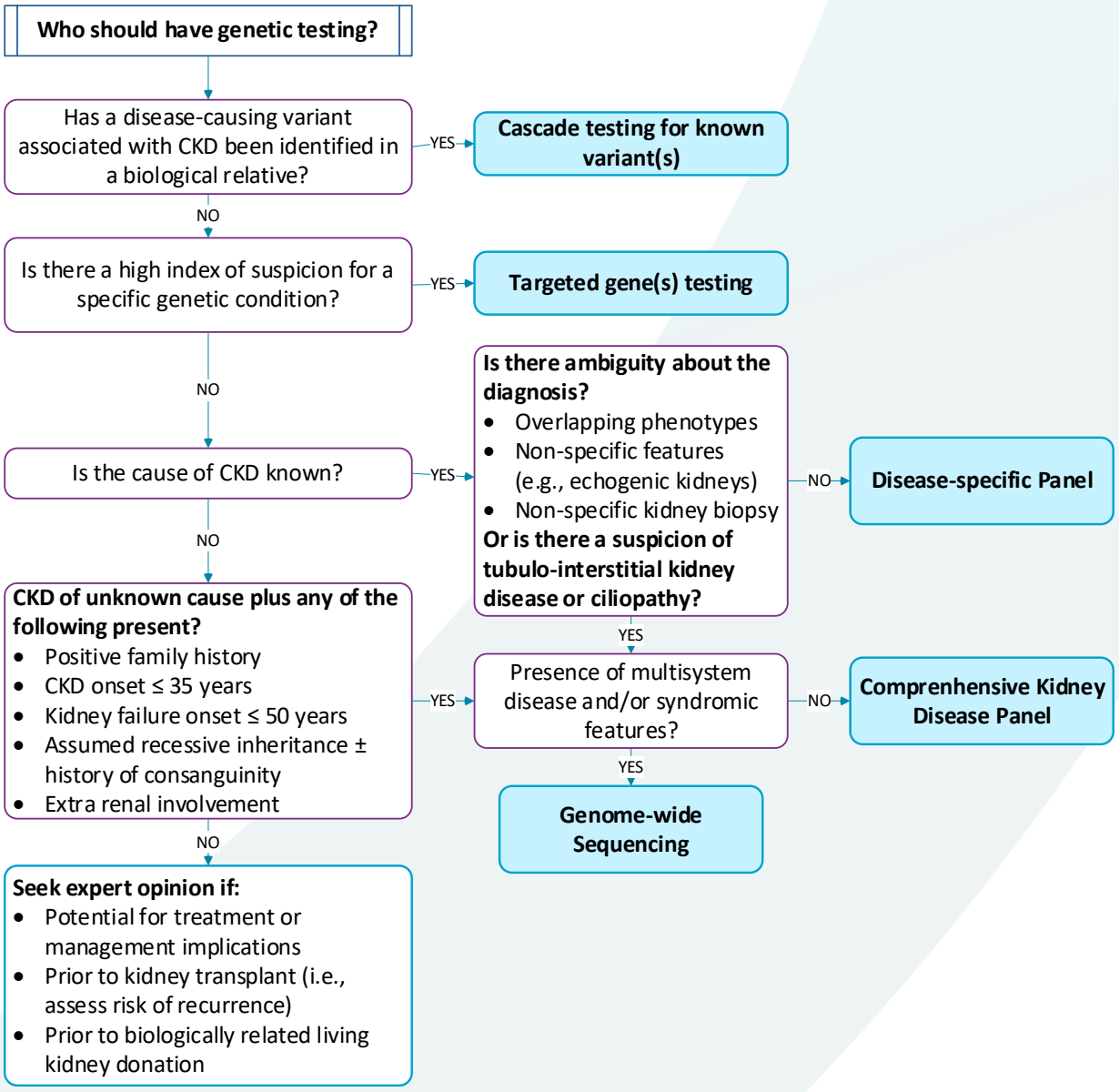
This guidance document outlines multigene panels, clinical eligibility criteria for genetic testing for individuals with CKD, including genome-wide sequencing (GWS) for select individuals with CKD.

Genetic Testing for Kidney Disease

Genetic testing for individuals with suspected genetic kidney disease in Ontario can follow multiple pathways, including known variant testing, targeted gene(s) testing, multigene panels, or GWS. Figure 1 summarizes these testing strategies and outlines key considerations for test selection.

Test selection should be driven by clinical judgement, informed by the patient's phenotype, family history, and diagnostic certainty. This section includes recommendations for each testing approach, including eligibility criteria and guidance to support clinical decision-making. In cases of diagnostic uncertainty, or when the appropriate testing strategy is unclear, consultation with a genetics specialist or multidisciplinary team should be considered.

Figure 1. Overview of the Different Strategies to Genetic Testing.



Note: Genome-wide sequencing refers to both genome and exome sequencing. CKD, chronic kidney disease.

Cascade Testing for Known Variants

Known variant cascade testing is recommended for close (i.e., first and/or second-degree relatives on the same side of the family) at-risk relatives following confirmation of a pathogenic or likely pathogenic variant in an individual[32]. Cascade testing supports early identification of heritable kidney disease, informs surveillance and management, and facilitates reproductive planning. Cascade testing should be conducted by professionals with expertise in genetics and/or heritable kidney diseases, with genetic counselling.

If the relative being assessed presents with an unusual phenotype, such as an atypical or more severe presentation of disease, or has a significant family history on the opposite side of the family, a broader strategy may be more appropriate than known variant testing.

When ordering cascade testing, every effort should be made to include the original test report of the relative with the known variant[33]. Ideally, cascade testing should be performed in the same laboratory that analysed the original relative's sample, or their sample should be sent alongside the at-risk relative's sample as a positive control.

Targeted Gene Testing

Targeted gene testing can be considered for individuals with CKD when there is a high(er) clinical suspicion for a specific genetic kidney condition. In such cases, the clinician may directly order testing for the relevant gene(s).

If the suspected genetic condition is unclear or if there is phenotypic overlap with other kidney diseases, a gene panel or GWS should be considered to reduce the chance of a missed diagnosis.

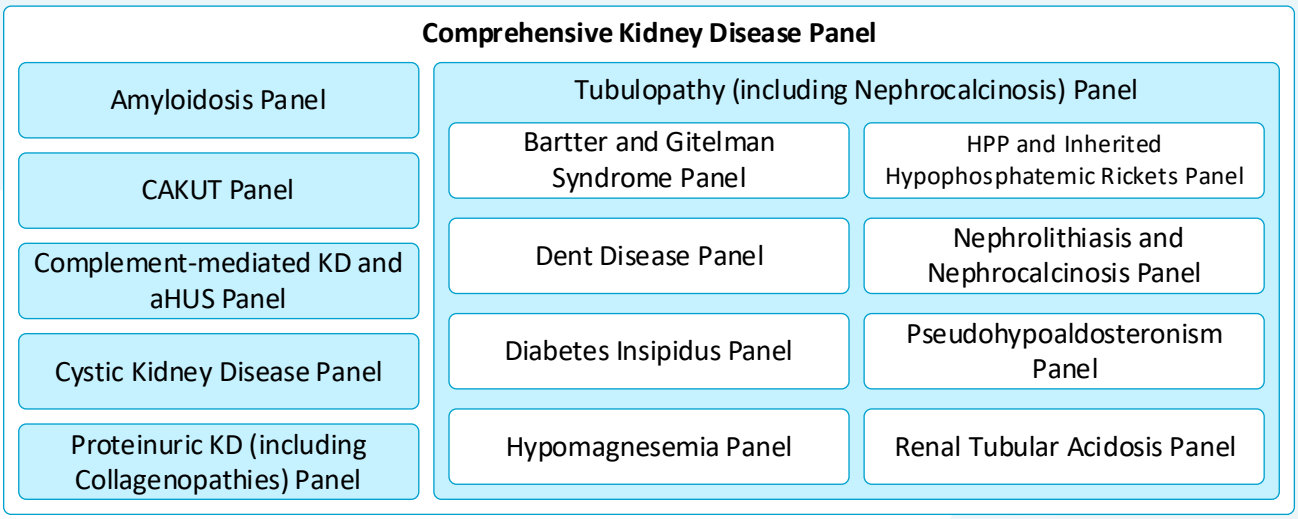
Examples of Targeted Gene(s) Testing Approach:

- Cystinosis[34]: *CTNS*
- Cystinuria[35]: *SLC3A1, SLC7A9*
- Fabry disease[36]: *GLA*
- Glomerulopathy with fibronectin deposits based on kidney biopsy report[37]: *FN1*
- Primary Hyperoxaluria[38]: *AGXT, GRHPR, HOGA1*
- Renal Cyst and Diabetes Syndrome[39]: *HNF1B*

Multigene Panels

Kidney disease genetic testing panels (Figure 2) are recommended when clearly indicated by the individual's clinical presentation and/or family history, in alignment with the eligibility criteria defined below. Each panel include genes associated with distinct subtypes of CKD and are designed to be sufficiently comprehensive to also capture clinically relevant genes with important phenotypic overlap. The gene contents of each panel can be found in Chronic Kidney Disease Multigene Panels.

Figure 2. Kidney Disease Genetic Testing Panels



aHUS, atypical hemolytic uremic syndrome; CAKUT, congenital anomalies of the kidney and urinary tract; HPP, hypophosphatemia; KD, kidney disease.

Amyloidosis Panel

Recommended for individuals with a strong clinical suspicion or clinical diagnosis of amyloidosis defined as the presence of:

- Abnormal amyloid deposits on a pathological specimen (i.e., kidney or skin biopsy), **and**
- Clinical features suggestive of hereditary amyloidosis, when other secondary causes have been ruled out[40]. These clinical features include, but are not limited to:
  - Restrictive cardiomyopathy[41]
  - Autonomic and peripheral neuropathy[42]
  - Gastrointestinal involvement[43]
  - Family history of amyloidosis[44]

Congenital Anomalies of the Kidneys and Urinary Tracts (CAKUT) Panel

CAKUT is defined as any abnormalities in the structure, function, size, shape, or position of the kidney and/or genitourinary tract[45]. Genetic testing is indicated for individuals with CAKUT **and** at least one of the following:

- Family history of CAKUT or unexplained kidney disease in a biological relative[45]
- Impaired kidney function, defined as a CKD-EPI stage ≥2[46]

Complement-Mediated Kidney Disease and Atypical Hemolytic Uremic Syndrome (aHUS) Panel

Recommended for individuals with CKD caused by any of the following:

- Dysregulation of the complement system[47]. Such patients may present with biopsy-confirmed membranoproliferative glomerulonephritis (MPGN), a glomerular injury pattern characterized by hypercellularity and thickening of the glomerular basement membrane (GBM)[48].
- Complement-mediated glomerulonephritis with either:
  - Family history of the condition
  - Need for genetic diagnosis to guide transplant management or treatment planning[47]

aHUS is characterized by acute kidney injury, thrombocytopenia, microangiopathic hemolytic anemia, and a negative Coombs test[49]. Genetic testing is recommended for individuals with a clinical diagnosis of aHUS, when there is any of the following:

- Family history of aHUS suggestive of a hereditary component
- C5 inhibitor therapy planning, as identifying pathogenic variants in complement genes informs the use of eculizumab or ravulizumab, which effectively inhibits terminal complement activation[50,51,52]
- Kidney transplant planning, as certain genetic variants are linked to a higher risk of post-transplant recurrence, aiding in risk assessment and perioperative management[53]

Cystic Kidney Disease Panel

A cystic kidney disease panel can be considered when there is a clinical suspicion for autosomal dominant polycystic kidney disease (ADPKD). ADPKD can be subdivided into classical or atypical presentations. Genetic testing should be considered as follows:

- Classical ADPKD: As per the KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD[54], diagnosis is typically supported by age-specific imaging criteria in individuals with a family history and enlarged kidney size (i.e., bilateral multi-cystic kidney disease)
- Atypical ADPKD: Genetic testing is indicated in all cases of atypical cystic kidney disease. Atypical cystic kidney disease is characterized by, but not limited to, fewer-than-expected cysts for age, asymmetrical or unilateral cyst distribution, normal or reduced kidney size, or absence of family history[55]

Genetic testing may be helpful to confirm the diagnosis, particularly in younger individuals, in families with variable disease severity, or when results would inform management, including reproductive decision-making or living kidney donor evaluation.

Individuals who are ineligible for genetic testing include presence of simple kidney cysts and normal kidney function.

Proteinuric Kidney Disease (Including Collagenopathies) Panel

This panel is indicated when any of the following criteria are met:

- Steroid-resistant nephrotic syndrome at any age[56,57]
- Proteinuria with focal segmental glomerulosclerosis (FSGS) or diffuse mesangial sclerosis (DMS) on kidney biopsy, particularly in cases with a family history of CKD, an unclear cause of proteinuria, or when a kidney transplant is planned and genetic testing is needed to assess post-transplant risk of recurrence[58]
- Glomerulonephritis of uncertain etiology, with clinical suspicion of a genetic cause[59,60]
- Persistent hematuria lasting more than six months with no obvious cause, and one of the following:
  - Family history of hematuria
  - Clinical and/or biopsy features suggestive of Alport disease or Alport syndrome, such as hearing impairment and/or eye pathology [61–63]

Tubulopathies (Including Nephrocalcinosis) Panel

Kidney tubulopathies are defined as diseases of the kidney tubule which lead to dysfunction in either water, electrolytes and/or acid-base homeostasis[64]. Genetic testing should be considered for individuals with any of the following:

- A clinical suspicion of a tubulopathy following full clinical and biochemical phenotyping, and exclusion of secondary causes[65]. Expert consultation is recommended for other rare tubulopathies.
- Radiologically confirmed nephrocalcinosis, after excluding acquired causes[66]
- Recurrent nephrolithiasis with a suspected genetic etiology[67], particularly when there is a family history or pediatric onset[68]

The tubulopathies panel encompass smaller sub-panels that could be considered when there is a high index of clinical suspicion for a specific condition in accordance with the eligibility criteria above. This includes panels for Bartter syndrome and Gitelman syndrome, Dent disease, diabetes insipidus, hypomagnesemia, hypophosphatemia, nephrolithiasis and nephrocalcinosis, pseudohypoaldosteronism, and renal tubular acidosis (Figure 2).

Comprehensive Kidney Disease Panel

The Comprehensive Kidney Disease Panel includes all the relevant CKD-related genes from the panels above, plus additional genes for tubulointerstitial kidney disease, ciliopathy, and select genes associated with syndromic presentations (i.e., syndromic CAKUT and nephronophthisis).

This panel is intended for individuals with CKD where the underlying genetic cause is unclear[38], complex, or spans multiple phenotypic categories. Expanded genetic testing may be warranted if targeted genetic testing, including a smaller panel, has not identified the underlying cause of disease and the likelihood of a genetic etiology is still considered high.

The following sections outline the eligibility criteria for the comprehensive kidney disease panel.

CHRONIC KIDNEY DISEASE OF UNKNOWN CAUSE (CKDU)

CKDu is defined as an eGFR of less than 60 mL/min/1.73 m² and the presence of kidney damage (including hematuria, proteinuria, or structural anomalies of the kidney and/or genitourinary tract), lasting for three months or longer, where no definitive primary kidney disease is identified[59,60]. This includes individuals with both positive and absence of family histories of kidney disease[16].

Genetic testing is recommended for individuals diagnosed with CKDu **and** one of the following:

- Diagnosed at ≤18 years, without an identifiable cause[69]
- ≤35 years old and have stage 3 or higher CKD
- Kidney failure onset before the age of 50 years[40,70]

Increasingly, data demonstrates the utility of genetic testing for individuals outside of these age ranges[18,19]. In line with KDIGO recommendations, there should be no upper age limit for monogenic kidney disease[21] and genetic testing can still be considered following expert consultation and/or when additional clinical information is available that may impact management.

CKD WITH OVERLAPPING KIDNEY PHENOTYPES

The comprehensive kidney disease panel may be considered when multiple kidney phenotypes are present and the underlying genetic cause is unclear. Genetic testing using the comprehensive panel is recommended when any of the following criteria are met:

- Clinical features suggest multiple CKD subtypes, and/or use of ≥2 kidney panels are anticipated
- Persistent unexplained hyperechogenicity of the kidneys on imaging (e.g., loss of corticomedullary differentiation)[71]
- Kidney biopsy is not feasible due to small size of the kidneys or advanced stage disease
- Kidney biopsy report is inconclusive or shows a non-specific pattern of injury[72]

TUBULOINTERSTITIAL KIDNEY DISEASE AND NEPHRONOPHTHISIS

Tubulointerstitial kidney disease is a genetically heterogeneous disorder characterized by progressive tubulointerstitial damage, subtle clinical features (e.g., progressive CKD, bland urine sediment), and a delayed onset of symptoms in adulthood, with an autosomal dominant pattern of inheritance[73]. Nephronophthisis, a genetically distinct yet clinically overlapping tubulointerstitial kidney disease, usually manifesting in childhood or adolescence, with a predominately autosomal recessive inheritance pattern. It leads to progressive renal fibrosis and cystic changes at the corticomedullary junction and may be associated with extra-renal features or multisystem disease[74].

Given their non-specific clinical presentation, the comprehensive kidney disease panel is indicated for individuals with CKD **and** clinical suspicion of tubulointerstitial kidney disease or nephronophthisis.

An important gene to consider is *MUC1*, associated with autosomal dominant tubulointerstitial kidney disease (ADTKD). The most common pathogenic variant is a cytosine insertion in a variable number tandem repeat region, accounting for approximately 95% of ADTKD-*MUC1* cases[75]Although *MUC1* is

included in the comprehensive kidney disease panel, the most common pathogenic variant is **NOT** detectable by standard sequencing platforms[76] or any currently available commercial panels from laboratories in or outside of Ontario. Data is emerging on enhanced detection strategies[77].

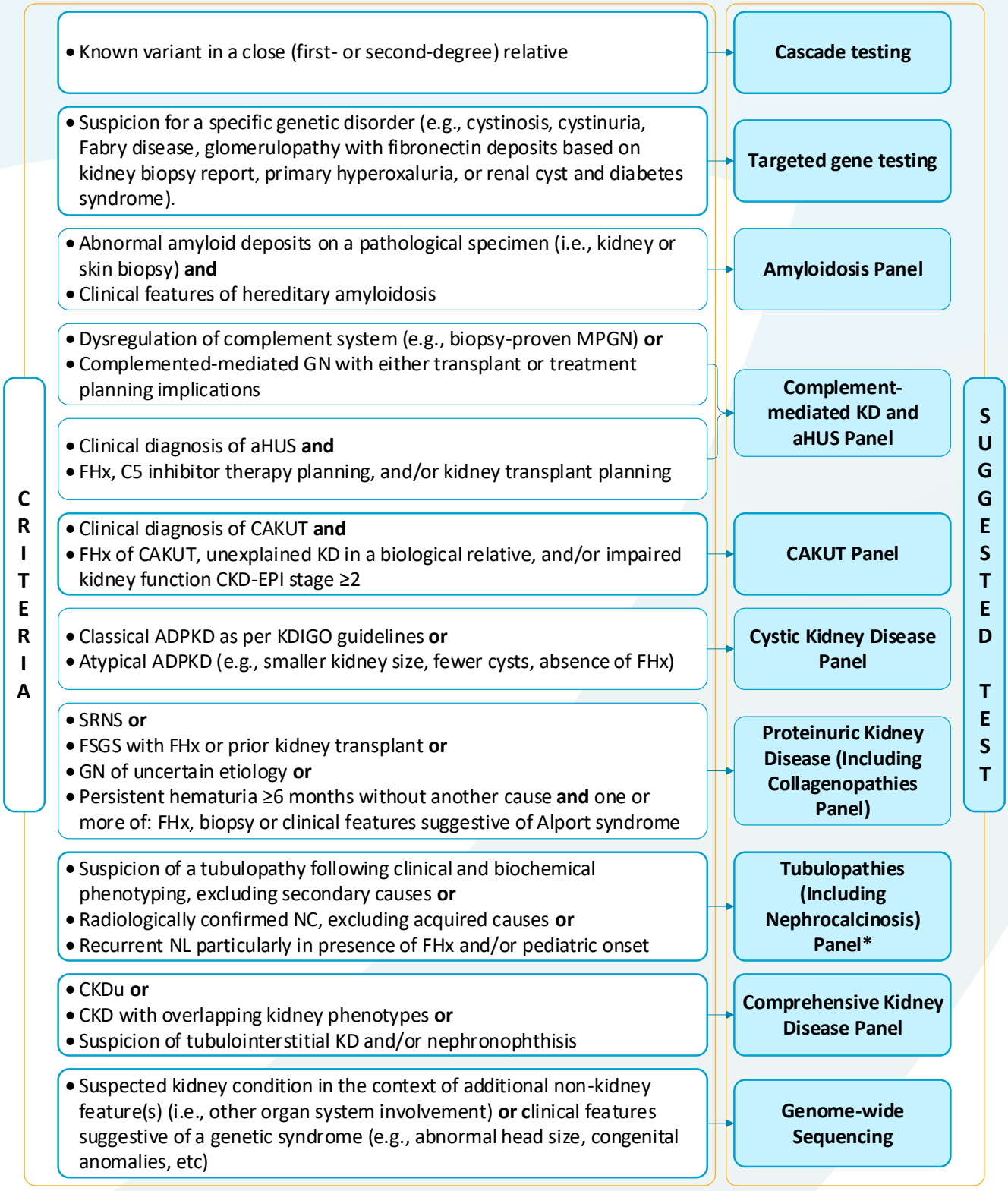
If ADTKD-*MUC1* variant is suspected, clinicians should seek kidney genetic expert advice through eConsult or a local genetics clinic before proceeding with testing[75].

Genome-wide Sequencing (GWS)

GWS, either exome or genome sequencing, can be considered in the following circumstances as the initial genetic testing approach:

- **Presence of a multisystem disease:** Suspected kidney condition in the context of additional non-kidney feature(s) (i.e., other organ system involvement).
- **Presence of a genetic syndrome:** Suspected kidney condition in the context of clinical features suggestive of a genetic syndrome including abnormal head size, additional medical comorbidities, congenital anomalies, distinctive physical features, neurodevelopmental disorders, and/or unexplained growth abnormalities (see Appendix A for expanded definitions).

Figure 3. Testing Options for Suspected Subtypes of CKD



ADPKD, autosomal dominant polycystic kidney disease; **aHUS**, atypical hemolytic uremic syndrome; **CAKUT**, congenital anomalies of the kidney and urinary tract; **CKD**, chronic kidney disease; **CKD-EPI**, Chronic Kidney Disease Epidemiology Collaboration; **CKDu**, chronic kidney disease of unknown etiology; **FHx**, family history; **FSGS**, focal segmental glomerulosclerosis; **GN**, glomerulonephritis; **KD**, kidney disease; **MPGN**, membraneproliferative glomerulonephritis; **NC**, nephrocalcinosis; **NL**, nephrolithiasis; **SRNS**, steroid resistant nephrotic syndrome.

Clinician Considerations

This section is intended to support clinicians in the delivery of genetic testing for individuals with suspected genetic kidney disease. It offers practical guidance on clinical scenarios around the use of genetic testing and interpreting and communicating results. These considerations aim to enhance confidence and clarity for clinicians navigating genetic testing for the first time or in complex cases.

Pre- and Post-test Counselling

Clinicians ordering genetic testing for their patients should provide appropriate pre-test counselling to facilitate informed decision-making. Pre-test discussions should include consent to testing, possible test outcomes, and test limitations. Following the disclosure of genetic test results, individuals with clinically relevant findings should be offered genetic counselling to discuss the implications of the results for themselves and their family[78]. Referral to a genetics professional may be appropriate to support these conversations, especially when results are complex or have broader familial implications.

Prior Genetic Testing

Before initiating genetic testing, the ordering clinician should confirm whether genetic testing has previously been performed on the index patient or any biological relatives. If prior testing has been conducted, every effort should be made to obtain and review the results prior to proceeding with further testing to avoid redundant testing and to ensure comprehensive interpretation.

If prior genetic testing has been performed on a genome or exome backbone and was uninformative, additional panel testing is generally unnecessary. In such cases, the clinician should consider reanalysis using a virtual, bioinformatic panel or, if clinically indicated, a reanalysis of the GWS data[79,80]. This avoids the need for a new sample collection, as the existing sequencing data can be re-interrogated based on updated clinical information, additional family data, or revised gene lists, particularly when a strong clinical suspicion of a genetic etiology persists.

Rapid Testing or Need for Rapid Diagnosis

Expedited genetic testing with a turnaround time of ≤ 1-3 weeks may be indicated when a rapid diagnosis is needed, particularly for:

- **Acutely unwell individuals:** In acutely unwell children or adults where monogenic kidney disease is suspected as the primary cause of disease, rapid genetic testing can be considered to confirm the diagnosis and guide urgent clinical decisions[81–83].
- **Rapid changes in management:** If genetic testing will lead to an immediate change in treatment[84], such as informing decisions about kidney transplant, therapeutic intervention[85], or prenatal testing for an at-risk pregnancy[86], rapid testing could be ordered as part of the clinical decision-making process. For example, in patients with clinical signs of primary hyperoxaluria type 1 post kidney transplant, the genetic diagnosis should be confirmed so that Lumasiran can be

administered to prevent further oxalate buildup, which can damage the transplanted kidney and other organs[87–89].

- **Neonates with Multiple Congenital Anomalies:** Rapid GWS testing could be considered in neonates presenting with multiple congenital anomalies including, at least, kidney anomalies consistent with CAKUT[90]. Early and rapid genetic testing can help identify the underlying genetic conditions that may guide treatment and management[91].

Clinicians should consider the urgency of the clinical situation, the likelihood of a genetic diagnosis, and the potential impact of results on immediate management when determining whether rapid testing is warranted. If a faster turnaround time is needed in situations where the individual is acutely unwell or there is an impact on management, contact the lab to discuss available options.

APOL1 Risk Allele Testing

Risk alleles are variants that are not necessarily disease-causing but can increase an individual's susceptibility to a particular disease or condition. *APOL1* has known risk alleles (i.e., homozygous for *APOL1* G1 or G2 allele, or compound heterozygous for G1/G2 confirmed in trans[92]) and has been included on the relevant panels where there are treatment and/or management implications.

Lab reports should clearly define the alleles that confer susceptibility as opposed to confirming disease diagnosis. Clinicians should exercise caution when interpreting the clinical significance of these variants and should ensure that patients are appropriately counselled on the implications of these findings. A referral to genetic counselling services may be warranted.

Testing Relatives for Variants of Uncertain Significance

A variant of uncertain significance (VUS) is defined by the American College of Medical Genetics (ACMG) Guidelines as a genetic variant with insufficient or conflicting evidence regarding its pathogenicity and therefore does not meet criteria for classification as benign, likely benign, pathogenic, or likely pathogenic[32]. A VUS should not be used in clinical decision-making[93]. Efforts to resolve the classification of a VUS to either pathogenic or benign may include familial segregation studies, functional assessments (if available), and reassessment of a variant over time as new data emerge[32,94]. If there is evidence suggesting that the interpretation may have changed, variant re-interpretation could be considered to ensure the classification remains up-to-date[13].

When a VUS is identified in a gene associated with a heritable kidney condition, it should be reviewed by a genetics professional or a clinician experienced in variant interpretation.

Testing close relatives for a VUS may assist in determining if the VUS segregates with the disease. It is important to note that although segregation analysis can be useful, in isolation it is often not sufficient to establish pathogenicity in the absence of other supporting data (e.g., population frequency, functional evidence, clinical correlation)[93].

In general, testing at-risk relatives with no kidney disease for a VUS is not recommended. However, it may be appropriate in specific situations such as determining if a variant is *de novo* (not inherited) when a VUS is suspected to contribute to disease, or to confirm phasing in autosomal recessive

conditions where testing can help determine if the variants are inherited in *trans* (on opposite alleles) or in *cis* (on the same allele) [93].

Clinical Judgment

Clinical judgment plays a critical role in determining if genetic testing may be appropriate, particularly in scenarios that fall outside of defined eligibility criteria. While standardized criteria support consistency and equity, test selection and the decision to test should be guided by a clinician's expertise and understanding of the individual's presentation, family history, and diagnostic certainty.

In some cases, expanded testing (i.e., a broader panel or genome-wide sequencing) may be appropriate following uninformative initial results. Conversely, clinicians may decide not to proceed with testing if the expected clinical benefit or diagnostic yield is low.

Consultation with a genetics professional or multidisciplinary team may be helpful to determine the appropriate testing strategy.

Clinician Resources to Support Interpretation of Genetic Testing Results

Clinicians who are uncertain about test selection, ordering process, result interpretation, or next steps are encouraged to seek expert consultation through available resources:

- Submit an eConsult request to connect with a genetics specialist through OTNhub.
- Consult gcConnect (1-844-564-4363, gcConnect@ontariohealth.ca) for genetic counsellor support of health care teams in navigating genetic services for their patients.
- Send a referral to your local genetics or kidney genetics clinic (Ontario Genetics Clinic Directory).
- Visit the Ontario Genetic Test Directory to find genetic tests available in Ontario.

Implementation Considerations

The following implementation considerations outline the system-level requirements and infrastructure needed to support the effective delivery of kidney genetic testing across Ontario. These considerations focus on setting up a system where genetic testing can be delivered equitably, efficiently, and consistently across the province.

Service Delivery Models

Genetic testing has historically been provided, following genetic counselling, by qualified geneticists, genetic counsellors, and physicians with specialized training and expertise in genetics. To improve timely and equitable access for patients with CKD, the standard is shifting towards a mainstreaming model, where non-genetics physicians involved in the diagnosis and management of kidney disease order genetic tests directly[95]. This approach facilitates earlier diagnosis and personalized treatment but requires that ordering physicians have a clear understanding of gene-based management guidelines to ensure appropriate pre-test counselling, test selection, result interpretation, and follow-up care. Ideally, these clinical pathways should be developed in collaboration with local kidney genetics experts to integrate genetic insights into routine nephrology practice and optimize patient outcomes[19,22,23,96]. To support the mainstreaming of kidney genetic testing ordering, clinicians, patients, and families should have access to educational tools and resources to allow for smooth transitioning to a new model of care.

Expanded Testing

If initial disease-specific panel testing does not identify a genetic cause of CKD, reflex testing to the comprehensive kidney disease gene panel or GWS should be considered, particularly when clinical suspicion remains high (e.g., family history or extra-renal features)[68]. Upon consultation with the laboratory and based on a reasonable likelihood of clinical benefit to the patient, ordering clinicians should be able to request expanded testing (i.e., additional gene panels or GWS) when initial multigene panel testing does not explain the patient's clinical presentation and symptomatology.

Laboratories should be equipped to support reanalysis of existing sequencing data and enable expanded testing without requiring new sample collection when appropriate.

Technical Requirements for Multigene Panels

The panels should capture the coding regions and flanking intron/exon boundaries and identify relevant copy number variants (CNVs) of all genes under analysis. Select relevant intronic variants should be included for the genes listed in the panel.

Laboratories should review the technical standards prior to implementation of the kidney disease panels. Technical limitations should be clearly communicated to ordering clinicians.

Genetic Testing Data Reporting

To support continuous improvement and equitable access, systems should be established to monitor the volume and types of kidney genetic tests ordered across regions and clinical settings. Outcome

reporting should include, at minimum, diagnostic yield and turnaround times. Efforts should be made to enable reporting into provincial data systems to allow assessment of clinical impact. These data can inform future updates to testing strategies and help identify gaps in service delivery.

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Appendices

Appendix A: Clinical Features Suggestive of a Genetic Syndrome

Abnormal head size: Occipitofrontal circumference 2 standard deviations above or below the mean for age, sex, and ethnicity (e.g., microcephaly, macrocephaly).

Additional medical comorbidities: Presence of additional medical conditions suggestive of a genetic basis (e.g., sensorineural hearing loss, vision impairment, cardiovascular disease, epilepsy, ataxia).

Congenital anomalies: A non-progressive morphological anomaly of a single organ or body part which is present at birth (e.g., cleft palate, polydactyly, congenital heart defect).

Distinctive physical features: Visible morphologic findings that differ from those commonly seen in the general population or within the same ethnic background (e.g., hypertelorism, syndactyly).

Neurodevelopmental disorders: Presence of global developmental delay or intellectual disability, particularly when co-occurring with congenital or early-onset kidney disease.

Unexplained growth abnormalities: Growth parameters 2 standard deviations above or below the mean for age, sex, and ethnicity (e.g., prenatal growth restriction, postnatal failure to thrive, short stature, overgrowth).

Appendix B: Abbreviations

ACMG	American College of Medical Genetics
AD	autosomal dominant
ADPKD	autosomal dominant polycystic kidney disease
ADTKD	autosomal dominant tubulointerstitial kidney disease
aHUS	atypical hemolytic uremic syndrome
AS	Alport syndrome
CAKUT	congenital anomalies of the kidney and urinary tract
CKD	chronic kidney disease
CKD-EPI	CKD Epidemiology Collaboration
CKDu	chronic kidney disease of unknown cause
CNV	copy number variant
DMS	diffuse mesangial sclerosis
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FHx	family history
FSGS	focal segmental glomerulosclerosis
GBM	glomerular basement membrane
GN	glomerulonephritis
GWS	genome-wide sequencing
KD	kidney disease
KDIGO	Kidney Disease Improving Global Outcomes
MPGN	membranoproliferative glomerulonephritis
NC	nephrocalcinosis
NL	nephrolithiasis
ORN	Ontario Renal Network
PGAC	Provincial Genetics Advisory Committee
PGP	Provincial Genetics Program
PKD	polycystic kidney disease
SRNS	steroid-resistant nephrotic syndrome
SSNS	steroid-sensitive nephrotic syndrome
VUS	variant of uncertain significance

Appendix C: Glossary

Please note that some definitions may have been extracted verbatim from the references included.

Chronic kidney disease (CKD): CKD is characterized by the presence of kidney damage or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2, persisting for 3 months or more[97].

Chronic kidney disease of unknown cause (CKDu): Chronic kidney disease, where no definitive primary kidney disease is identified[60].

Copy number variant (CNV): Duplication or deletion of a section of DNA. CNVs can be benign (normal), pathogenic, or of uncertain clinical significance, and are also known as a structural variant[98].

End-stage kidney disease (ESKD) synonmous with kidney failure: End-stage renal disease is a terminal stage of the disease that is defined as a eGFR of less than 15 mL/min[99].

Estimated glomerular filtration rate (eGFR): A mathematically derived entity based on a patient's serum creatinine level, age, sex, and race[100].

Exome sequencing: A next generation sequencing test that reads the DNA sequence of most of the protein-encoding exons and the exon-intron boundary in an individual[101].

Gene panel: A genetic test that analyzes multiple specific genes simultaneously to identify variants associated with a particular disease or group of related conditions.

Genome sequencing: The use of next-generation sequencing technology to read through all the nucleotides and not just exons[102].

Genotype: The genetic constitution of an organism or cell; also refers to the specific set of alleles inherited at a locus[103].

Index Patient: The affected individual through whom a family with a genetic disorder is ascertained; may or may not be the individual presenting for genetic counselling[103].

Phenotype: The observable physical and/or biochemical characteristics of the expression of a gene; the clinical presentation of an individual with a particular genotype[103].

Reflex: Follow-up testing automatically initiated when certain test results are observed in the laboratory; used to clarify or elaborate on primary test results[103].