Controversies Conference on APOL1 Kidney Disease

Moving towards routine APOL1 genetic testing: ethical implications in kidney transplantation

Rulan S. Parekh MD, MS, FRCPC
Vice-President, Research, Innovation and Education
Women's College Hospital
Professor of Medicine, Pediatrics and Epidemiology
University of Toronto
• Relationships with commercial interests:
  • Grants/Research Support: NIH, CIHR, Ministry of Education
  • Speakers Bureau/Honoraria: None
  • Consulting Fees: Vertex
Case

• Medical student wanted to donate to her mother who has been on dialysis for 2 years
  • She finds out she is a carrier for high-risk APOL1 haplotype
  • She is prevented from donating to her mother
  • But no one can tell her own long-term risk and what she needs to do to prevent chronic kidney disease
  • And if she donates, no one can tell her long-term risk of progression to CKD with a single kidney
  • She now feels like a “ticking time bomb”
  • No one has considered that she may lose her mother given the high mortality rate on dialysis and long waits for deceased donor transplant
Case

- Medical student wanted to donate to her mother who has been on dialysis for 2 years
  - She finds out she is a carrier for high-risk APOL1 haplotype
  - She is prevented from donating to her mother clinical utility when research is pending
  - But no one can tell her own long-term risk and what she needs to do to prevent chronic kidney disease Understanding risk when prevalence and penetrance varies and other gene or environmental factors are important
  - And if she donates, no one can tell her long-term risk of progression to CKD with a single kidney medical uncertainty
  - She now feels like a “ticking time bomb” psychological impact of testing
  - No one has considered that she may lose her mother given the high mortality rate on dialysis and long waits for deceased donor transplant what is actionable?
  - She questioned whether she should have had testing
Considerations for genetic testing
## APOL1 testing in US transplantation

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
</table>
| 2024 | Delphi Consensus of 27 patients, donors, surgeons, nephrologists and genetic counsellors (majority self-identified as Black/African American)  
     | Development of a chatbot to provide results |
| 2023 | Focus groups of 10 transplant nephrologists |
| 2022 | Survey of 331 potential living donors, recipients, waitlisted persons and also non transplant patients in 3 transplant programs |
| 2020 | 585 participants self identified as African American from the general population using simulated questions on risk |
| 2019 | 17 African American donors from a single center through 4 focus groups to assess impact on treatment, sociocultural factors and health benefits |
| 2018 | 23 African American donors from a single center focus groups/survey |
| 2017 | Transplant Expert Panel |
Consistent findings among all studies

• Autonomy in testing is critical
• Return of results and decision making based on those results are shared with patient and clinician
• Education is vital for patients, families, and all clinicians
• Engagement with patients, families and communities is vital for any study
  • Ensures culturally appropriate education and type of methods
  • Addresses concerns of study design, approach and returning of results
• Differences by region are rarely addressed
• How education, perceptions and beliefs may alter shared decision making globally is unknown
Evaluating ApoL1 Genetic Testing Policy Options for Transplant Centers
A Delphi Consensus Panel Project with Stakeholders

Tristan McIntosh,1 Heidi Walsh,1 Kari Baldwin,1 Ana Ilitis,2 Sumit Mohan,1
Melody Goodman,3 and James M. DuBois1


The Road to APOL1 Genetic Testing in Transplantation

Rulan S Parekh1

• Community Advisory Council
• https://www.apollocommunity.net/
Evaluating ApoL1 Genetic Testing Policy Options for Transplant Centers: A Delphi Consensus Panel

Conclusions: The panel supported policy options involving discussion and shared decision making among patients, donors, and family stakeholders. There was opposition to unilateral decision making by transplant programs and prohibiting donation altogether.

Africa is not monolithic and variability in prevalence of APOL1 differs between countries and within ethnic groups. Admixture in the Caribbean and Brazil and Hispanic persons suggest that screening is important in this group as well. Admixture is increasing globally. Should genetic testing to only those that self-report African ancestry. Did not address the psychological stress as a result of uncertainty of risk. Raises the issue of ongoing education given evolving epidemiology of APOL1.
Implementation of a culturally competent \textit{APOL1} genetic testing programme into living donor evaluation: A two-site, non-randomised, pre-post trial design

Justin D Smith \textsuperscript{1,2}, Akansha Agrawal \textsuperscript{3}, Catherine Wicklund \textsuperscript{4}, Debra Duquette \textsuperscript{3}, John Friedewald \textsuperscript{3}, Luke V Rasmussen \textsuperscript{5}, Jessica Gacki-Smith \textsuperscript{6}, S Darius Tandon \textsuperscript{7}, Lutfiyya N Muhammad \textsuperscript{8}, Clyde W Yancy \textsuperscript{9}, Siyuan Dong \textsuperscript{10}, Matthew Cooper \textsuperscript{11}, Alexander Gilbert \textsuperscript{12}, Aneesha Shetty \textsuperscript{13}, Elisa J Gordon \textsuperscript{14}

Affiliations + expand
PMID: 37188469  PMCID: PMC10186444  DOI: 10.1136/bmjopen-2022-067657

Development of a culturally targeted chatbot to inform living kidney donor candidates of African ancestry about \textit{APOL1} genetic testing: a mixed methods study

Elisa J Gordon \textsuperscript{1}, Jessica Gacki-Smith \textsuperscript{2}, Matthew J Gooden \textsuperscript{2}, Preeya Waite \textsuperscript{2}, Rochell Yacat \textsuperscript{3}, Zenab R Abubakari \textsuperscript{3}, Debra Duquette \textsuperscript{4}, Akansha Agrawal \textsuperscript{8}, John Friedewald \textsuperscript{9}, Sarah K Savage \textsuperscript{6}, Matthew Cooper \textsuperscript{7,8,9,10}, Alexander Gilbert \textsuperscript{3}, Lutfiyya N Muhammad \textsuperscript{11}, Catherine Wicklund \textsuperscript{12}

Affiliations + expand
PMID: 38349598  PMCID: PMC11031529  DOI: 10.1007/s12687-024-00698-8

- Community Advisory Board
- Scientific Advisory Board
A National Survey of Transplant Surgeons and Nephrologists on Implementing Apolipoprotein L1 (APOL1) Genetic Testing Into Clinical Practice

Elisa J Gordon ², Catherine Wicklund ³, Jungwha Lee ³, Richard R Sharp ⁴, John Friedewald ⁵

Affiliations + expand
PMID: 30541404  PMCID: PMC8527710  DOI: 10.1177/1526924818817048

A Focus Group Study on African American Living Donors' Treatment Preferences, Sociocultural Factors, and Health Beliefs About Apolipoprotein L1 Genetic Testing

Elisa J Gordon ², Daniela Amórtegui ², Isaac Blancas ², Catherine Wicklund ³, John Friedewald ⁴, Richard R Sharp ⁵

Affiliations + expand
PMID: 31146624  DOI: 10.1177/1526924819854485
**Determining the effects and challenges of incorporating genetic testing into primary care management of hypertensive patients with African ancestry**

C R Horowitz, N S Abul-Husn, S Ellis, M A Ramos, R Negron, M Suprun, R E Zinberg, T Sabin, D Hauser, N Calman, E Bagiella, E P Bottinger

**Effects of Testing and Disclosing Ancestry-Specific Genetic Risk for Kidney Failure on Patients and Health Care Professionals: A Randomized Clinical Trial**

Girish N Nadkarni, Kezhen Fei, Michelle A Ramos, Diane Hauser, Emilia Bagiella, Stephen B Ellis, Saskia Sanderson, Stuart A Scott, Tatiana Sabin, Ebony Madden, Richard Cooper, Martin Pollak, Neil Calman, Erwin P Bottinger, Carol R Horowitz
RCT: Effects of Testing and Disclosing Ancestry-Specific Genetic Risk for Kidney Failure on Patients and Health Care Professionals

**Populaton**
690 Men, 1360 Women

Adults with African ancestry with hypertension and without existing chronic kidney disease
Mean age, 53 y (range, 18-70 y)

**Intervention**
2050 Randomized

1795 Intervention group
Patients received APOLI genetic testing results from trained staff who used clinical decision support

255 Control group
Control patients received APOLI genetic testing results after a 12 mo follow-up visit

**Findings**
Patients with high-risk APOLI genotypes had significantly higher change in SBP compared with low-risk APOLI and control groups and higher urine screening compared with controls but not with patients with low-risk APOLI genotypes

**Settings/locations**
15 Academic, community, and safety-net practices in 2 US health care systems

**Primary Outcome**
Coprimary outcomes were change in systolic blood pressure (SBP) at 3-mo and 12-mo urine kidney disease screening between Patients with high-risk APOLI genotypes and patients with low-risk APOLI genotypes

Need more research......

• Consider clinical context
  • CKD, FSGS or transplant donor/ recipient
  • Actionable vs not actionable
  • Diagnostic vs predictive
  • Overall disease prevalence which may alter test characteristics
  • Consider who gets tested
  • Economic impacts of testing
  • Gaps in knowledge lead to more uncertainty

• Address regional differences in ethical, social and legal implications
Multiple frameworks to approach data to move genetic testing into clinical use
<table>
<thead>
<tr>
<th>TABLE S-1 Comparison of Frameworks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method</strong></td>
</tr>
<tr>
<td>USPSTF</td>
</tr>
<tr>
<td>Fryback-Thornbury</td>
</tr>
<tr>
<td>ACCE</td>
</tr>
<tr>
<td>Method</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>EGAPP</td>
</tr>
<tr>
<td>GETT</td>
</tr>
<tr>
<td>McMaster University</td>
</tr>
<tr>
<td>Frueh and Quinn</td>
</tr>
</tbody>
</table>

## Genetic/genomic testing: defining parameters for ethical, legal and social implications (ELSI)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sub-criteria</th>
</tr>
</thead>
</table>
| Ethical  | Patient rights | Right to health  
|          |               | Free and informed consent  
|          |               | Knowing or not knowing results and implications  
|          |               | Respect for privacy and confidentiality  
|          |               | Respect for human dignity  
|          | Non-discrimination | Avoid genetic reductionism  
|          |               | Genetic exceptionalism  
|          |               | Avoid stigmatization  
| Legal    | Protection of the Information | Actions to ensure the protection of biological samples, and all physical and electronic information  
|          | Testing | Circumstances of application  
|          | Health regulation | Advantages, disadvantages and limitations  
|          | Surveilance | Qualified health personnel  
|          | Medical-patient-company responsibility | Surveillance  
|          | Countries responsibility | Medical-patient-company responsibility  
|          | Analytical validity | Countries responsibility  
|          | Validity and clinical utility | Analytical validity  
|          | Laboratory accreditation | Validity and clinical utility  
|          | Commercialization | Laboratory accreditation  
|          | Direct-to-consumer testing | Commercialization  
|          | Medical tourism | Direct-to-consumer testing  
|          | Advertising | Medical tourism  
|          | Cross-border business | Advertising  
| Social   | Counseling | Cross-border business  
|          | Pre-clinical and post-results | Counseling  
|          | In clinic | Pre-clinical and post-results  
|          | Training | Education and dissemination  
|          | Reporting of Results | Concept of health and disease  
|          | Communication of the risks | Training  
|          | Unexpected findings | Reporting of Results  
|          | Accessibility | Unexpected findings  
|          | Access to services under the principle of justice | Accessibility  

1. Universal Declaration on the Human Genome and Human Rights, UNESCO 1997  
2. Oviedo Convention, Council of Europe 1997  
3. Review of Ethical Issues in Medical Genetics, WHO 2003  
4. International Declaration on Human Genetic Data, UNESCO 2003  
5. Declaration of Reykjavik, WMA 2019  
6. Medical genetic services in Developing Countries. The Ethical, Legal, and Social Implications of Genetic Testing and Screening, WHO 2006  
Ethical questions to consider for APOL1 genetic testing among those with CKD, FSGS or transplant donor/recipient

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sub-criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethical</td>
<td>Patient rights</td>
</tr>
<tr>
<td></td>
<td>Right to health</td>
</tr>
<tr>
<td></td>
<td>Free and informed consent</td>
</tr>
<tr>
<td></td>
<td>Knowing or not knowing results and implications</td>
</tr>
<tr>
<td></td>
<td>Respect for privacy and confidentiality</td>
</tr>
<tr>
<td></td>
<td>Respect for human dignity</td>
</tr>
<tr>
<td>Non-discrimination</td>
<td>Avoid genetic reductionism</td>
</tr>
<tr>
<td></td>
<td>Genetic exceptionalism</td>
</tr>
<tr>
<td></td>
<td>Avoid stigmatization</td>
</tr>
</tbody>
</table>
Legal questions to consider for APOL1 genetic testing among those with CKD, FSGS or transplant donor/recipient

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sub-criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legal</td>
<td>Protection of the Information</td>
</tr>
<tr>
<td></td>
<td>Actions to ensure the protection of biological samples, and all physical and electronic information</td>
</tr>
<tr>
<td>Testing</td>
<td>Circumstances of application</td>
</tr>
<tr>
<td>Health regulation</td>
<td>Advantages, disadvantages and limitations</td>
</tr>
<tr>
<td>Commercialization</td>
<td>Qualified health personnel</td>
</tr>
<tr>
<td></td>
<td>Surveillance</td>
</tr>
<tr>
<td></td>
<td>Medical-patient-company responsibility</td>
</tr>
<tr>
<td></td>
<td>Countries responsibility</td>
</tr>
<tr>
<td></td>
<td>Analytical validity</td>
</tr>
<tr>
<td></td>
<td>Validity and clinical utility</td>
</tr>
<tr>
<td></td>
<td>Laboratory accreditation</td>
</tr>
<tr>
<td></td>
<td>Direct-to-consumer testing</td>
</tr>
<tr>
<td></td>
<td>Medical tourism</td>
</tr>
<tr>
<td></td>
<td>Advertising</td>
</tr>
<tr>
<td></td>
<td>Cross-border business</td>
</tr>
</tbody>
</table>
23andMe Offers a New Report on APOL1-Related Chronic Kidney Disease

August 5, 2020 By 23andMe under Health and Traits

Today, 23andMe added a new Genetic Health Risk report on APOL1-related chronic kidney disease that has particular relevance for customers with African ancestry.

Relevant ethnicities

- The variants included in this test are most common and best studied in people of African descent.
- These variants are also found in people with African ancestry, including people of Hispanic or Latino descent.
Social questions to consider for APOL1 genetic testing among those with CKD, FSGS or transplant donor/recipient

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sub-criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social</td>
<td>Pre-clinical and post-results</td>
</tr>
<tr>
<td></td>
<td>In clinic</td>
</tr>
<tr>
<td>Counseling</td>
<td>Education and dissemination</td>
</tr>
<tr>
<td>Training</td>
<td>Concept of health and disease</td>
</tr>
<tr>
<td>Reporting of Results</td>
<td>Communication of the risks</td>
</tr>
<tr>
<td></td>
<td>Unexpected findings</td>
</tr>
<tr>
<td>Accessibility</td>
<td>Access to services under the principle of justice</td>
</tr>
</tbody>
</table>
Need more research
Indigenous framework for genetic testing
Advancing health equity
Language, narrative and concepts

- American Medical Association and Association of American Medical Colleges
- Advancing Health Equity: Guide on Language, Narrative and Concepts...
- ama-assn.org/equity-guide
# Informed use of race, ethnicity and ancestry

<table>
<thead>
<tr>
<th></th>
<th>Equity focused alternative</th>
<th>Commonly used</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>Self-ascribed</td>
<td>Black</td>
<td>System of categorizing people that arises to differentiate groups of people in hierarchies to advantage some and disadvantage others.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>black</td>
<td></td>
</tr>
<tr>
<td>Self-ascribed</td>
<td>white</td>
<td>Caucasian</td>
<td>Associated Press recommends not capitalizing white, recognizing that “white people generally do not share the same history and culture, or the experience of being discriminated against because of skin color.”</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Self-ascribed</td>
<td>African</td>
<td>Social construct and category based on shared geography, language, ancestry, traditions or history. Boundaries of authenticity (that is, who or what “counts” in recognizing members of an ethnic group) are often changeable and dependent on generational, social, political and historical situations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Americans</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>West Africans</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Country</td>
<td></td>
</tr>
<tr>
<td>Ancestry</td>
<td>Gene variants/ genome</td>
<td></td>
<td>Genetic ancestry is the genetic origin of one’s population. Genetic admixture, or genetic exchange among people from different ancestries, is an important characteristic of many populations and may correlate with individuals’ risk for certain genetic diseases</td>
</tr>
</tbody>
</table>
Conflation of genetic ancestry and race

• “Genetic data have led clinical investigators to focus on \textit{APOL1} polymorphisms as a key, rather than a contributory, explanatory variable in racial disparities in kidney disease.....This approach, however, is based upon a misapplication of population genetics and exacerbated by conflation of genetic ancestry and race”

Vanessa Grubbs
Using Population Descriptors in Genetics and Genomics Research

A New Framework for an Evolving Field

Consensus Study Report
1. Population descriptor ≠ group label.
A population descriptor is a way to classify individuals according to perceived differences among groups; a group label is a specific name used to describe a population.

2. Researchers often use population descriptors inconsistently and/or inappropriately.
Race, for example, should not be used for analysis in most genomics studies. It may be used for some health disparities studies.

3. Genetic ancestry refers to the lines or paths through an individual’s family tree by which they inherited DNA from specific ancestors. It can be useful when studying human evolutionary history.

4. Genetic similarity, a measure of genetic resemblance among individuals, is preferred in many other contexts because it moves away from race and the misconception that humans can be grouped into discrete categories.

Sometimes funders require collection of Office of Management and Budget (OMB) Standards categories to report demographic information of research participants, but use of OMB categories is not required for scientific analysis.
Updated Guidance on the Reporting of Race and Ethnicity in Medical and Science Journals

Annette Flanagan, RN, MA; Tracy Frey, BA; Stacy L. Christiansen, MA; et al.

Editorial
August 17, 2021

CMAJ’s new guidance on the reporting of race and ethnicity in research articles

Matthew B. Stanbrook and Bukola Salami

Guidance on Use of Race, Ethnicity, and Geographic Origin as Proxies for Genetic Ancestry Groups in Biomedical Publications

W Gregory Feero, Robert D Steiner, Anne Slavotinek, Tiaa Goel, Michael J Barnshad, Jehannine Austin, Bruce R Korf, Annette Flanagan, Kirsten Bibbins-Domingo

Affiliations + expand
PMID: 38470200 DOI: 10.1001/jama.2024.3737
Case

• Medical student wanted to donate to her mother who has been on dialysis for 2 years
  • She finds out she is a carrier for high-risk APOL1 haplotype
  • She is prevented from donating to her mother clinical utility when research is pending
  • But no one can tell her own long-term risk and what she needs to do to prevent chronic kidney disease understanding risk when prevalence and penetrance varies and other gene or environmental factors are important
  • And if she donates, no one can tell her long-term risk of progression to CKD with a single kidney medical uncertainty
  • She now feels like a “ticking time bomb” psychological impact of testing
  • No one has considered that she may lose her mother given the high mortality rate on dialysis and long waits for deceased donor transplant what is actionable?
  • She questioned whether she should have had testing
Need more research

- Recommendations
  - All studies should include patient and community engagement to inform approach from research questions to knowledge translation
  - Address specific ELSI criteria to generate evidence for ongoing testing
    - Actionable vs not actionable
    - Diagnostic vs predictive
    - Specific clinical scenarios ie transplant vs CKD vs FSGS
  - Consider changing populations locally and globally
  - Genetic information is only one contributor to account for underlying disparities in health
  - Reporting using new guidance will improve our reporting
Thank you
Trials for APOL1

A first-in-human study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of AZD3270 after single dose administration in healthy male subjects of African ancestry.

JUSTICE is a single-center, double-blinded, randomized trial of baricitinib therapy for APOL1-associated FSGS or hypertension associated-CKD.

Design and rationale of GUARDD-US: A pragmatic, randomized trial of genetic testing for APOL1 and pharmacogenomic predictors of antihypertensive efficacy in patients with hypertension.
Who are carriers of $APOL1$ risk variants?
Volume and direction of the trans-Atlantic slave trade-
12,521,337 Africans were enslaved
Frequency of *APOL1* risk variants vary worldwide

Higher prevalence in regions reminiscent of slave trade patterns
Self-reported identity of high-risk $APOL1$ carriers

- Cross-sectional studies among Hispanic/Latino communities
  - NYC
    - Diabetic ESRD 6%
    - Non-Diabetic ESRD 20%
  - Hispanic Community Health Study/Study of Latinos
    - Caribbean/mainland 0.004%

Genetic Ancestry of African Americans, Latinos, and European Americans across the United States

A

B

C

D

Self-reported African Americans with > 2% Native American ancestry

The American Journal of Human Genetics Volume 96 Issue 1 Pages 37-53 (January 2015)
‘We’re talking about a big, powerful phenomenon’: Multiracial Americans drive change

While still a relatively small part of the population, more Americans than ever identify as multiracial, according to the census

By Silvia Foster-Frau, Ted Mellnik and Adrian Blanco
October 8, 2021 at 8:00 a.m. EDT

More people say they are multiracial

Here’s how census numbers on race changed from 2010 to 2020

- Multiracial: +24.8 million
- White alone: +23.6 million
- Other race alone: +6.8 million
- Asian alone: +5.4 million
- Black alone: +2.3 million
- Native American alone: +0.8 million

Multiracial population growth in metropolitan areas
Brief Communication

Transplant Nephrologists’ Preferences for Clinical Decision Support for APOL1 Genetic Testing of Living Kidney Donors: A Focus Group Study

Luke V. Rasmussen 1, Akamba H. Agrawal 1, and Elisa J. Gordon 1

2022


Apolipoprotein L1 Opinions of African American Living Kidney Donors, Kidney Transplant Patients, and Nonpatients

Dwight D Harris 1, Aaron Fleishman 1, Martha Pavlakis 2, Martin R Pollak 2, Prabhakar K Baliga 2, Vinayak Rohan 3, Liise K Kayler 4, James R Rodrigue 5

Opinions of African American adults about the use of apolipoprotein L1 (ApoL1) genetic testing in living kidney donation and transplantation

Margaret Berndt 1, 2 | Janine Austin 1, 2 | Aaron Fleishman 1, 2 | Kenneth P. Toronto 2 | Martin R. Pollak 2, 5 | Martha Pavlakis 2, 3 | Vinayak Rohan 2 | Prabhakar K. Baliga 2 | Liise K. Kayler 4 | Thomas H. Fesley 1 | James R. Rodrigue 2, 5

2021
African American Living Donors' Attitudes About APOL1 Genetic Testing: A Mixed Methods Study

Elisa J Gordon 1, Daniela Amórtegui 2, Isaac Blancas 2, Catherine Wicklund 3, John Friedewald 4, Richard R Sharp 5

Integrating APOL1 Gene Variants Into Renal Transplantation: Considerations Arising From the American Society of Transplantation Expert Conference