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Genetic Testing in Clinical Settings

Nora Franceschini, M.D., M.P.H.[1], **Amber Frick, Pharm.D., Ph.D.**[2], and **Jeffrey B. Kopp, M.D.**[3]

[1]Department of Epidemiology, Gillings School of Public Health, University of North Carolina, Chapel Hill, NC

[2]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC

[3]Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Abstract

Genetic testing is used for screening, diagnosis and prognosis of diseases consistent with a genetic etiology, and to guide drug therapy to improve drug efficacy and to avoid adverse effects (pharmacogenomics). This *in practice* aims to inform on DNA-related genetic test availability, interpretation, and recommended clinical actions based on results using evidence from clinical guidelines, when available. We discuss challenges that limit the widespread use of genetic information in the clinical care setting, including a small number of actionable genetic variants with strong evidence of clinical validity and utility, and the need for improving the health literacy of health care providers and public including for direct-to-consumer tests. Ethical, legal and social issues and incidental findings also need to be addressed. Because our understanding of genetic factors associated with disease and drug response is rapidly increasing, and new genetic tests are being developed that could be adopted by clinicians in the short term, we also provide extensive resources for information and education on genetic testing.

Keywords

genetic testing; pharmacogenetics; kidney disease; APOL1; drug selection; drug dosing; risk allele; pharmacokinetics; ancestry; mutation; polymorphism; pharmacogenomics; gene variant; review

Overview of genetic testing

The US National Institutes of Health (NIH) defines genetic testing as an analysis of human chromosomes, genes, or proteins in order to detect heritable disease for clinical purposes.[2]

Address correspondence to:Nora Franceschini, M.D., M.P.H., University of North Carolina, Gillings School of Public Health, Chapel Hill, NC, 137 E. Franklin St. #306, noraf@unc.edu, Phone: (919) 966-1305.

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This definition does not include tests used for research purposes. Genetic testing has been traditionally used for pre-natal screening, screening for carriers of a genetic disorder for reproductive purpose, and diagnosis of rare Mendelian disorders suspected based on clinical evidence or family history. Recent advances in high-throughput genomics have made large-scale genotyping and sequencing affordable. This has led to an increased number of genetic tests being developed, including tests for clinical use and commercially available direct-to-consumer genetic tests.[3] In the emerging field of pharmacogenomics, genetic testing is proposed to guide drug therapy to improve drug efficacy or to avoid adverse effects. However, there are still several challenges that limit the widespread use of genetic information in the clinical care setting.

This review aims to inform on new developments on the field, including available tests, their utility to patients, as well as regulatory and ethnic issues related to genetic testing. We will focus on molecular genetic tests, the purpose of which is to identify DNA variation, including both polymorphisms (which are usually not pathogenic) and mutations that are associated with genetic disorders. We will cover genetic testing for Mendelian disorders, complex traits such as *APOL1* (apolipoprotein L1)-associated CKD, and pharmacogenomics.

We will not address genetic testing for prenatal and newborn screening, diagnosis of rare or atypical diseases in newborns including chromosomal abnormalities, diagnosis of somatic mutations (DNA changes that occur after conception, e.g., in cancer), or genetic tests for metabolic diseases. The American College of Medical Genetics and Genomics (ACMG) provides practice guidelines that cover these topics (Table 1).

Because our understanding of genetic factors associated with disease and drug response is expected to rapidly increase in the next few years, and new genetic tests are being developed that could be adopted by clinicians in the short term, we also provide extensive resources for information and education on genetic testing (Table 1).

Type of genetic tests

Several types of genetic tests are available including single-variant tests (e.g., diagnosis of the *HBB* p.Glu7Val mutation [a substitution of valine for glutamine at amino acid 7 of beta globin] that causes sickle cell disease), gene-based tests (single or multiple genes, e.g., genetic testing for autosomal dominant polycystic kidney disease [ADPKD] mutations in the *PKD1* and *PKD2* genes), and genetic panels (e.g., for genetic variants associated with drug metabolism). Genetic tests cover single-nucleotide variants, haplotypes (e.g., HLA region), deletion/insertion variants, copy number variants, and mutations in mitochondrial DNA. Whole-exome sequencing and whole-genome sequencing use next-generation sequencing (NGS) methods of high-throughput DNA analysis to identify Mendelian disorders when clinical features and family history are consistent with a genetic etiology.

Whole-exome sequencing with confirmation of relevant genetic variants by Sanger sequencing may be the most cost-effective approach to genetic clinical diagnosis when multiple loci are possible explanations for a particular syndrome. However, this approach

may identify mutations for which the clinical significance has not been established (variants of unknown significance, or VUS) for which return of results to patients is uncertain.[4] Genome-wide genotype arrays and whole-genome sequencing are also available as direct-to-consumer products for disease risk prediction in individuals without a suspected genetic condition. The clinical utility of these tests in asymptomatic healthy individuals is unclear, and there are potential harms related to reporting incidental findings and/or genetic variants for which the clinical consequences are unknown, e.g., VUS.[5]

Genetic test validity and utility

In choosing a genetic test, one needs to assess the following: (1) how well the test performs to detect the genetic variation or mutation of interest (technical performance), (2) how well the variant or mutation tested accurately and reliably predicts the clinical disease (clinical validity), and (3) what is the evidence that the genetic test improves clinical outcomes or has added value for patient management decisions (clinical utility) (Figure 1). These criteria for the evaluation of a genetic test are based on the Center for Disease Control and Prevention ACCE model, which also includes ethical, legal, and social implications of genetic testing (Table 1).

In the United States, the technical performance or safety and effectiveness of a test is regulated by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act as medical devices for tests sold as kits. However, for tests marketed as a laboratory-developed test and performed by a single laboratory, the FDA has practiced “enforcement discretion”. The Centers for Medicare and Medicaid Services (CMS) is responsible for regulating the clinical laboratories performing genetic testing in the U.S., ensuring their compliance with Clinical Laboratory Improvement Amendments (CLIA). Some tests are also regulated by states. The sequencing and interpretation pipeline is accredited by the College of American Pathologists (CAP).

The clinical validity of a test depends on the evidence of the variant’s association with disease, and includes functional information for the variant tested, i.e., loss of function mutations that disrupt the function of protein-coding genes are more likely to influence phenotypes or lead to a clinical disease. However, the function of many variants is unclear. The ClinVar archive at the National Center for Biotechnology Information (NCBI) lists known human genetic variants and provides information about which variants have been associated with human disease, and which ones have no phenotype identified to date for interpretation of the clinical significance of variants found in patient samples including pathogenicity. The evidence for clinical validity of variants listed in ClinVar varies (Table 1).

The clinical utility is the evidence that the test improves clinical outcomes and therefore helps with patient management decisions. For example, most tested variants have little evidence from randomized clinical trials to establish their clinical utility.

Online genetic variant registries

The MEDLINE resources of the National Library of Medicine include another highly useful repository of genetic information that pertain to gene, diseases and diagnoses, in addition to

ClinVar. The Online Mendelian Inheritance in Man (OMIM) includes human genes and genetic phenotypes and despite its name, is not restricted to genes with Mendelian inheritance. Currently, over 15,000 disorders are listed.

Genetic test indications

Mendelian disorders

Several Mendelian and mitochondrial disorders have kidney phenotypes that manifest at childhood or adulthood and may initially go undiagnosed. These disorders result from mutations that have high penetrance (proportion of individuals presenting with the disease or phenotype among carriers of the mutation and the mode of inheritance) and varying expressivity (different clinical/pathologic manifestations from mild to severe disease). Their diagnosis may have implications for therapy and screening of family members for counseling or for kidney donation.

Mendelian disorders result from complex mutations in genes, which provide challenges for genetic testing. The choice to pursue genetic testing should be guided by the benefit of the knowledge obtained. For example, highly penetrant mutations in over 50 different genes in nuclear or mitochondrial DNA have been identified for focal segmental glomerulosclerosis (FSGS).[6] Children with FSGS due to genetic mutations are less likely to respond to glucocorticoids and less likely to have disease recurrence after kidney transplantation. Whole-exome sequencing is a more comprehensive approach for diagnosis of these mutations unless there is a known mutation segregating in families. There is a need for more studies on the clinical validity and utility of genetic testing for patients and families, particularly when the test is used for screening of genetic causes of FSGS.

For some known genetic disorders, there may be an alternative method of diagnosis for the disease. For example, ADPKD is the most commonly diagnosed inherited kidney disease, accounting for 5-10% of all patients on renal replacement therapy (recently reviewed by Chebib and Torres[7]). Most cases of ADPKD are due to mutations in the *PKD1* (80-85%) and the *PKD2* (15-20%) genes. Recently, mutations in the *GANAB* gene were identified in whole-exome sequencing in affected family members [8] and mutations in an additional seven genes were identified for hereditary polycystic kidney and liver disease.[9] Over 2,300 and 270 mutations have been reported for the *PKD1* and *PKD2* genes, respectively.[9a] These can be tested using Sanger sequencing, NGS, and commercially available testing services.[10] However, in clinical practice, ADPKD diagnosis is based on imaging of the kidneys and age-related ultrasound diagnostic criteria, or use of alternative kidney imaging such as magnetic resonance imaging or computed tomography rather than genetic testing.[11] This is because genetic testing may not provide a definitive diagnosis if detected mutations have unknown pathogenicity, the frequency of mutation detection often is equivalent to the frequency of disease detection by imaging, and there are issues related to cost and insurance coverage of the test. A recent KDIGO (Kidney Disease: Improving Global Outcomes) conference recommended genetic testing in special situations such as for diagnosis of ADPKD when renal imaging is inconclusive, in cases of early and severe clinical presentation and those with a negative family history (potential *de novo* mutations), and for

screening in the setting of reproductive counseling.[11] Genetic testing in these cases usually includes consultation with genetic medical experts and genetic counselors.

APOL1-associated CKD

APOL1 G1 and G2 alleles are African-ancestry specific variants recently identified as risk factors for CKD. [12,13] G1 encodes two highly correlated nonsynonymous (amino acid changing) variants, whereas G2 encodes a 6-nucleotide deletion. Small indels (insertions or deletions of bases in the genome) such as G2 can be captured using sequencing, although different platforms have different reliability for indels. Individuals carrying two *APOL1* risk genotypes (high-risk; about 13% of African Americans[12,13] and 2% of U.S. Hispanics/Latinos of Caribbean background[14]) have an increased risk for end-stage kidney disease (odds ratio of ~ 7) and for FSGS (odds ratio of 10 to 29 including HIV nephropathy).[12,13] Among CKD participants of the African American Study of Kidney Disease and Hypertension (AASK), *APOL1* high-risk carriers had a 1.9-fold risk of a composite outcome of ESRD or a doubling of the serum creatinine level.[15] However, among African Americans in the general population, *APOL1* high-risk status was associated with 1.5-fold risk for CKD.[16]

Using published data on *APOL1* and CKD in African Americans, we estimated the sensitivity and specificity, and the likelihood ratios (LR) that a test result would be expected in a patient with disease compared to a patient without disease using different scenarios related to the purpose of the test (Figure 2). When genetic testing is performed for diagnosis, a positive *APOL1* test result has moderate to low LR (true positive/false positive) for FSGS and ESRD, respectively, and would only increase the probability of disease by ~30%. However, a negative test can be useful to rule out *APOL1*-related FSGS disease and therefore for counselling. When *APOL1* is tested in African Americans at-risk of CKD or progression to later stages of CKD, a positive test has a low true positive to false positive ratio, and is not helpful for screening or prognosis of CKD. A negative test in these settings is also not helpful, as it cannot discriminate a true negative from a false negative result (LR close to 1). These are due to differences in the magnitude of the genotype-disease association (odds ratio) and prevalence of the disease in these different settings.

In contrast to Mendelian disorders described above, the disease penetrance of *APOL1*-related CKD is low, with only about 20% of individuals carrying high-risk genotypes developing CKD,[17] and there is a large variability in clinical disease manifestations and progression among those developing CKD. With regard to kidney transplantation, recipients of donor kidneys obtained from individuals carrying high-risk *APOL1* genotypes may have shorter allograft survival.[18] A critical question that is an area of active investigation relates to the frequency of *APOL1* high-risk alleles in CKD in living donors and the etiologic role that these variants might play.

Importantly, the clinical and environmental factors leading to development of *APOL1*-related CKD and effective therapies for prevention or treatment of individuals at risk are not yet established. Screening of individuals for *APOL1* alleles for prognosis will require assessments of the risk/benefit of genetic testing in the clinical setting and engagement of patients and African American communities in these medical decisions, given potential

harms.[19] There is currently insufficient evidence to recommend genetic testing of *APOL1* for diagnosis and prognosis of CKD. To answer some of the questions related to organ donation, NIH recently established the Long-term Kidney Transplantation Outcomes Research Network (APOLLO), which will assess the role of *APOL1* genetic variants as susceptibility factors in kidney transplant recipients of organs from African American donors, and the clinical outcome of kidney donors who carry *APOL1* variants.

Pharmacogenetics

Overview—Genes influence the response to pharmacologic agents and genetic tests may help to guide treatment strategies such as avoiding side-effects and other harmful complications. Genetic testing may provide information on drug effectiveness (e.g., non-responders) and effects on drug metabolism (faster versus slower metabolizers) that could allow individualized drug dose. In addition, pharmacogenetic testing can be used to identify individuals who are at-risk of severe idiosyncratic adverse events, therefore helping in medical decisions for choice of therapy including using alternative strategies for treatment. Although there has been great interest in pharmacogenetics, there is a large gap in the knowledge on actionable variants (those which results can change treatment), and the use of genetic testing in clinical care is still limited to few variants and drugs.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international consortium that develops peer-reviewed guidelines for pharmacogenetic testing based on evidence from randomized controlled trials and other clinical studies.[20] CPIC recommendations focus on gene-drug pairs for CLIA-approved genetic tests that show evidence for the need to change drug dose or consider an alternative drug but does not recommend whether a test should be ordered. So far, CPIC has published 36 pharmacogenetic drug guidelines that includes variants in 15 genes.

Table 2 summarizes the CPIC guidelines (updated at https://cpicpgx.org/guidelines/) for genetic testing for selected drug-gene pairs that have strong levels of evidence based on clinical validity and utility. Below we discuss a few examples of pharmacogenetic testing based on clinical indication.

Genetic testing to guide drug dose—Genetic variants can alter drug-metabolism (pharmacokinetics) and therefore guide drug dose adjustments to avoid under-treatment or side effects from high drug exposure. For example, the oral anticoagulant warfarin, widely used for the prevention and treatment of thromboembolic disorders, has large inter-individual variability in dosing to achieve therapeutic range related to both dietary and genetic factors. Warfarin has a narrow therapeutic range, and both low and high international normalized ratio (INR) can be harmful. Testing for genetic variants in genes related to warfarin metabolism (*CYP2C9*), the target enzyme for warfarin action (*VKORC1*, described in the section on genetic testing for drug effectiveness) and in pathways related to vitamin K recycling (*CYP4F2*) are currently recommended by CPIC to guide the dosing of warfarin.[21] Variants in these three genes account for up to 18%, 30%, and 11%, respectively, of the variability in warfarin dose in individuals of European ancestry. Genetic testing is available

for *CYP2C9**2 and *3 (more common in European ancestry; *CYP2C9**2 is absent in Asians), *CYP2C9**5, *6, *8, and *11 (more common in African ancestry), and *CYP4F2**3.

Genetic testing to guide drug choice—Genetic testing can help treatment decisions by identifying sensitivity or resistance to drugs used for the condition being treated (drug effectiveness). For example, ivacaftor is an FDA-approved drug for cystic fibrosis that regulates the activity of the cystic fibrosis transmembrane conductance regulator (CFTR) channel and has been shown to improve lung function in clinical trials.[22] Approximately 85-90% of individuals of European ancestry with cystic fibrosis carry at least one copy of the F508del variant, which is a functional variant that leads to an abnormal CFTR protein. Individuals carrying two copies of the *CFTR* F508del mutation showed no improvement in clinical symptoms or in lung function after ivacaftor treatment (non-responders), and an alternative treatment is recommended for these patients. Additional variants associated with lack of response to the drug and variants associated with drug efficacy (33 *CFTR* variants) are shown in Table 2. Current guidelines recommend genetic testing for *CFTR* variants before initiation of ivacaftor treatment based on clinical efficacy studies.[23,24]

Another example of genetic variants affecting drug response and currently recommended for genetic testing are variants in the *VKORC1* gene, which encodes the enzyme vitamin K epoxide reductase, the target for the oral anticoagulant warfarin. A common variant in *VKORC1* (reference single-nucleotide polymorphism [rs] identifier 9923231, 1639G>A [substitution of guanine by adenine at nucleotide 1639]) is associated with increased sensitivity to warfarin. Patients who carry this variant require lower doses of warfarin to achieve the target INR. Rare protein-changing variants in *VKORC1* have shown to confer warfarin resistance but are usually not tested for. Guidelines for dose drug adjustments based on the common *VKORC1* variant and other genetic variants related to warfarin pharmacokinetics have been recently updated (Table 1).[21] It is expected that additional genetic testing will be developed to guide the choice of drugs based on drug efficacy in clinical care.

Genetic testing to avoid idiosyncratic drug events—Adverse events may themselves result in morbidity and, in severe cases, mortality, and can contribute to drug treatment non-adherence. Some adverse events with underlying genetic susceptibility (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug-induced liver disease) may be prevented by genetic testing.[25] For example, genetic testing is already integral to the use of some antiretroviral agents in HIV clinical care management in the U.S.[26] Abacavir is generally well-tolerated; however it may cause an immunologically mediated hypersensitivity reaction driven by activation of *HLA-B**57:01.[27,28] Abacavir hypersensitivity reactions related to *HLA-B**57:01 occur in 3 to 5% of patients during the first 6 weeks of treatment.[29] Testing for the *HLA-B**57:01 allele is now recommended by the FDA before initiating antiviral treatment that includes abacavir based on results of PREDICT-1 (Prospective Randomized Evaluation of DNA Screening in a Clinical Trial).[30] The trial randomized HIV-infected patients to a prospective-screening group, which excluded *HLA-B**57:01–positive patients from abacavir treatment, or a control group, which used a standard-of-care approach to abacavir use without prospective screening.

Immunologically confirmed hypersensitivity reactions occurred in 0% in the prospective-screening group vs. 2.7% in the control group (P<0.001), with a NPV of 100% and a positive predictive value (PPV) of 47.9%. Additional studies have shown the cost-effectiveness of testing for *HLA-B**57:01 before starting abacavir treatment.[31-33]

Genetic testing for *HLA-B**15:02 is recommended before using the anticonvulsant drug carbamazepine to avoid life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis. Individuals with one or two copies of the *HLA-B**1502 allele, which is common in Oceanic, East Asian, and South/Central Asian populations (1 to 10%) but not in Europeans, are at risk of cutaneous reactions, and avoidance of the drug is recommended for patients not previously exposed to the drug.[34]

Information on commercially available genetic testing

The Genetic Testing Registry (GTR) is a NIH-developed voluntary registry of genetic tests and genetic testing services, both academic and commercial. GTR includes information on the test's purpose, methodology, validity, usefulness, and laboratory contacts and credentials (Table 1). The information on quality and utility for clinical use of tests available in this database varies. The most recent data from GTR from December 2017 shows 54,290 tests for 16,406 genes and 10,974 conditions performed by 509 labs. As an example, 16 clinical tests for *APOL1* are currently listed at GTR, offered by 12 CLIA-certified laboratories. Seven are a single gene test for *APOL1*, at a cost of $200 to $1,000, and include whole-gene sequencing, sequencing of *APOL1* exon 6 only, or direct genotyping of G1/G2 variants. Information on positive and negative results are not provided, and the reporting of VUS that will likely will be identified in sequencing data varies.

Direct-to-consumer testing

Healthcare attitudes continue to shift towards empowering patients, who have become more proactive in managing their care. As a result, direct-to-consumer genetic testing has become a popular option. The FDA has expressed concern over direct-to-consumer tests being used by the public to self-diagnose without the intervention of healthcare providers, potentially leading to self-treatment or cessation of current medication.[35] In recent years, the FDA has sent warning letters to direct-to-consumer genetic test companies, including 23andMe and DNA4Life, stating that their genotyping tests needed approval as a medical device prior to marketing.[36-38] Both of these companies genotype pharmacogenomic variants, and in the United Kingdom, 23andMe still provides results for some pharmacogenomics tests. Direct-to-consumer pharmacogenomics testing is unique in that results become actionable once a drug is prescribed, ranging from the point of testing or potentially many years later, leading to advocacy for preemptive genotyping pharmacogenomics panels. Arguably, direct-to-consumer genotyping will act as a powerful conduit for integrating pharmacogenomics into practice as evidence for its clinical utility is being collected.[39] With the expansion of such testing, educational initiatives on direct-to-consumer genotyping are essential to improving the health literacy of healthcare providers and the public.[40]

Challenges and limitations of genetic testing

Some of the challenges related to the adoption of genetic testing for diagnosis and treatment of patients are the lack of demonstrated clinical validity and utility of some genetic variants (such as most of the genetic variants identified in genome-wide association studies) and the existence of alternative approaches that have lower costs (e.g., dosing blood levels of the drug instead of adjusting based on genetic testing). For a limited number of variants with strong evidence for preemptive screening, mostly in pharmacogenomics, efforts should focus on increased access of information for health care providers through education on test availability, interpretation, and recommended clinical actions based on results, including existing guidelines from CPIC and/or scientific societies. For example, pharmacogenomic tests could be reported as positive (see Table 2 for list of variants) with recommendations on clinical actions. Concerns related to patient safety due to incorrect test ordering, misinterpretation and lack of follow-up of findings have also been raised[41]. Incorporating genetic testing into electronic medical records will facilitate genetic-driven clinical medical decisions.

Most diseases or traits including CKD are polygenic, i.e., influenced by multiple genes. Therefore, genetic panel testing including several variants may be more efficient for use in screening and diagnosis of genetic disease and in pharmacogenomics. Because the prevalence of variants varies in ancestral populations and some variants may be rare in some ethnic groups, genetic testing will likely be more cost-effective if targeting patients from a racial/ethnic group with a high prevalence of the variant. For example, the *HLA-B**57:01 allele related to abacavir toxicity is common in European ancestry individuals (allele frequency of 8%) but rare in individuals of African ancestry (0.3%).[42] Conversely, genetic panels including variants from multiple ancestral populations will be more suitable for widespread use in clinical care in countries with a large ancestry admixture such as the U.S.

Ethical and legal aspects

The implementation of genetic testing in clinical care will require establishing a facile process for ordering genetic testing in hospital and clinics, access to expertise to address ethical, legal community, patient, and family concerns,[19] in addition to information on cost and coverage by insurance. To address concerns related to discrimination of individuals for insurance purpose or by society, anti-discrimination laws have been passed in the U.S. These include the Genetic Information Nondiscrimination Act (GINA), which prevents insurers and employers from using genetic information in decisions about health-care coverage or employment, and the Patient Protection and Affordable Care Act, which blocks insurers from denying coverage or raising premiuems due to pre-existing conditions. Some of the challenges on implementation of genetic testing are being studied in the National Institutes of Health-funded Implementing GeNomics In practice (IGNITE) Network. [43]

Discussion with patients and families

Discussions with patients and families should be tailored to the specific purpose for ordering the genetic test (diagnosis, prediction, screening) and guided by information on risk and

benefits in these settings. Topics include discussion on whether the genetic results will alter the clinical management of the patient or provide information important for the care of the patient or family members who may carry the genetic mutation, alternative options to genetic testing, and costs. Engagement of a genetic counselor both before ordering the test and when test results are available is recommended, as these counselors have familiarity with testing technical procedures and interpretation of results, and extensive experience in providing counseling to families and in addressing patients' concerns. Genetic testing for *APOL1* is currently controversial outside research settings, with little evidence available on benefits or harms that would support specific recommendations. African American patients should be informed on the limited evidence for clinical utility of the genetic testing of *APOL1* variants for CKD, and the current lack of specific treatment for CKD patients who are tested positive. Discussion should also include the lack of data on the utility of *APOL1* genetic testing for screening CKD in healthy African Americans including kidney donors.

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Case study

A 67-year-old white male with CKD stage G3, coronary heart disease, hypertension and hyperlipidemia was started on allopurinol 300 mg/d for gout.[1] Additional medications were metoprolol, simvastatin, enalapril and aspirin. After one week of allopurinol treatment, nausea and a skin rash developed. He was admitted to the hospital three days later with a generalized maculopapular exanthema, fever to 39°C, and a perip heral leukocyte count of 24,000 cells/μL with 20% eosinophils. His right great toe had red swelling and was painful. Serum creatinine was 1.8 mg/dl (160 μmol/l) and urinalysis was negative for nitrites and positive for leukocytes. Broad spectrum antibiotics were started. Blood and urine cultures all gave negative results. He received a diagnosis of allopurinol-induced hypersensitivity and was started on prednisolone 1 mg/kg/d. His symptoms improved sufficiently to be discharged from the hospital after two weeks. However, his skin lesions had not healed and he was admitted six weeks later with sepsis and multi-organ failure.

Case Review

Allopurinol-induced hypersensitivity is an uncommon and devastating adverse effect of allopurinol, which has a 25% mortality rate.[44] Allopurinol reactions can manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), and severe cutaneous adverse reactions (SCAR). This patient has clinical and laboratory findings compatible with allopurinol hypersensitivity syndrome. Two case series have described hypersensitivity following exposure to allopurinol in 78 individuals[45] and 101 individuals.[37] Common features are erythematous skin rash, eosinophilia, hepatitis, and reduced kidney function. The treatment of allopurinol hypersensitivity syndrome is mostly supportive and includes future avoidance of the drug. Oxypurinol, the active metabolite of allopurinol, is involved in allopurinol-associated hypersensitivity by inducing T-cell response and hypersensitivity. An *HLA-B**58:01 variant has been associated with hypersensitivity to allopurinol and has an allele frequency of 6-7% in Asian populations (particularly those in East Asia) and 1% in European descent populations.[44] The odds ratio for hypersensitivity associated to allopurinol with the *HLA-B**58:01 allele is estimated to be 80 to 580:1. Other risk factors include recent initiation of therapy and impaired renal function, which elevates levels of allopurinol and oxypurinol. Oxypurinol preferentially binds to the peptide binding groove of *HLA-B**58:01,[44] and likely forms a drug-peptide-HLA complex that is highly immunogenic, initiating the hypersensitivity reaction. The 2012 American College of Rheumatology Guidelines for treatment of gout recommends preemptive genetic testing for patients of Korean descent with CKD stage 3 or worse (allele frequency of 5%), and persons of Han-Chinese or Thai descent irrespective of kidney function.[46] The 2015 updated CPIC guidelines states that allopurinol is contraindicated in persons of any ethnicity with a positive genetic test for *HLA-B**58:01.[47] In light of the morbidity and mortality of allopurinol-associated hypersensitivity, testing for *HLA-B**58:01 variants is indicated prior to allopurinol therapy initiation. In the case study, genetic testing was not performed, and so a role for *HLA-B**58:01 cannot be known for certain.

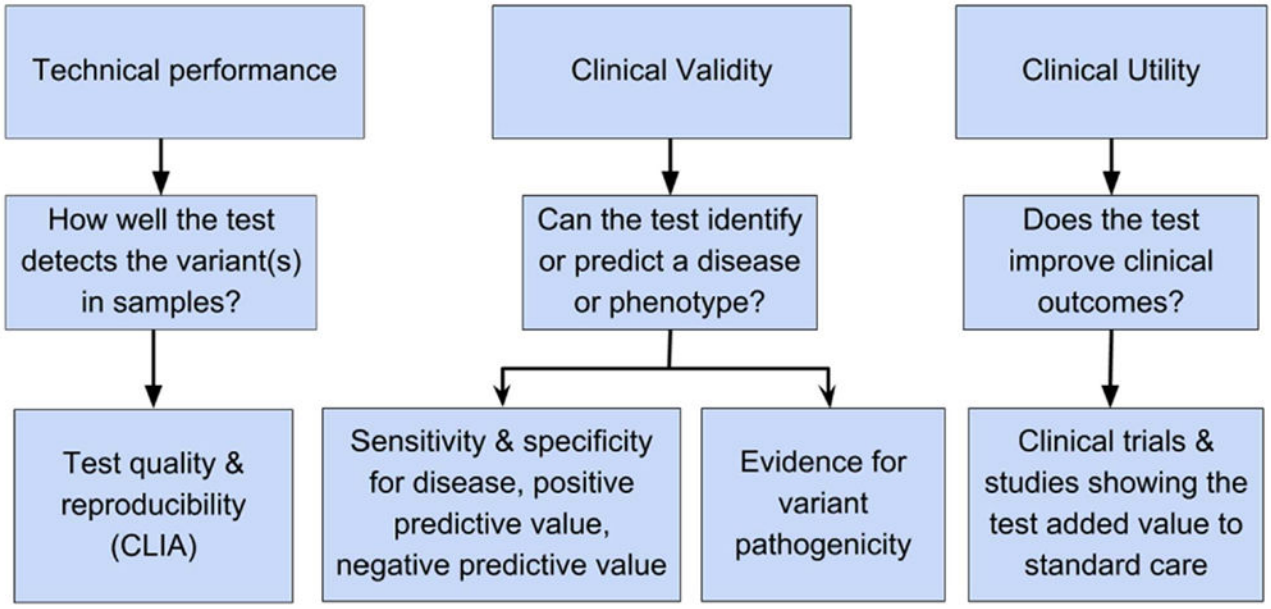

Figure 1.

Evaluation of a clinical test. The three aspects that need to be evaluated are technical performance, clinical validity and utility. Each aspect relates to a distinct function of the test (second row) and yields data on particular aspects of test performance and utility (third row).

A FSGS case and controls

	FSGS	Controls	Total
APOL1 +	127	22	149
APOL1 -	65	154	219
Total	192	176	368

OR 10.5
Sensitivity 0.66
Specificity 0.88
+ LR 5.3 (3.5, 7.9)
- LR 0.4 (0.3, 0.5)

B ESRD case and controls

	ESRD	Controls	Total
APOL1 +	466	109	575
APOL1 -	536	814	1350
Total	1002	923	1950

OR 7.0
Sensitivity 0.47
Specificity 0.88
+ LR 3.9 (3.3, 4.8)
- LR 0.6 (0.6, 0.6)

C AASK African Americans without diabetes

	CKD progression*	Controls	Total
APOL1 +	93	67	160
APOL1 -	195	338	533
Total	288	405	693

OR 1.9
Sensitivity 0.32
Specificity 0.83
+ LR 2.0 (1.5, 2.6)
- LR 0.8 (0.7, 0.9)

D African Americans from the general population

	Incident CKD**	Controls	Total
APOL1 +	33	371	404
APOL1 -	157	2506	2663
Total	190	2877	3067

OR 1.5
Sensitivity 0.17
Specificity 0.87
+ LR 1.3 (1.0, 1.9)
- LR 0.9 (0.9, 1.0)

Figure 2. Clinical validity of *APOL1* testing for disease diagnosis and prognosis in African Americans

We estimated the sensitivity, specificity, positive likelihood ratio (+LR, true positive/false positive) and negative likelihood ratio (-LR, true negative/false negative) for *APOL1* testing (and 95% confidence intervals) using published data. The settings designated as A and B are related to FSGS and ESRD diagnosis, respectively. C and D are genetic testing used for prognosis. The +LR is moderate to low when a genetic testing is performed for diagnosis of *APOL1*-related FSGS (A) and ESRD (B), respectively, and so a positive test may be useful only for diagnosis of *APOL1*-related FSGS. The -LR is close to zero in setting A, so a negative test could help to rule out *APOL1*-related FSGS. When testing African Americans with non-diabetic CKD (C) or screening African Americans without CKD in the general population (D), the +LR is low, supporting the low yield for an *APOL1* genetic testing used for prognosis or screening. In addition, a negative test is not helpful to rule out future disease or counseling in settings C and D since the -LR is close to 1. Data obtained from table 1 in Genovese *et al*[12] (A & B), table 2 in Parsa *et al*[15] (C) and table 2 in Foster *et al*[16] (D). *APOL1* + is high-risk genotypes and *APOL1* – is low risk genotypes. We assumed the disease is causally related to *APOL1* high-risk genotypes, although other genetic variants could contribute to CKD. *incident ESRD or doubling of serum creatinine **An eGFR < 60 ml/min/1.73 m^2 at follow-up

Table 1

Resources for information on genetic testing

Source	Information provided	Website or reference
ACMG: The American College of Medical Genetics and Genomics guidelines	Practice guidelines based on disease topics and policy statements regarding genetic testing.	http://www.acmg.net/ACMG/Publications/Practice_Guidelines/ACMG/Publications/Practice_Guidelines.aspx?hkey=
ASHG: The American Society of Human Genetics	Genetic testing educational resources	https://www.ashg.org/education/genetic_testing.shtml
Centers for Disease Control and Prevention	ACCE model for evaluating genetic tests	https://www.cdc.gov/genomics/gtesting/ACCE/
Center for Disease Control and Prevention	EGAPP recommendations	https://www.cdc.gov/genomics/gtesting/egapp/recommend/index.htm
Center for Disease Control and Prevention	Direct-to-consumer information	https://blogs.cdc.gov/genomics/2017/04/18/direct-to-consumer-2/
CPIC: Clinical Pharmacogenetics Implementation Consortium	Pharmacogenetics guidelines	https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC
NCBI ClinVar	Online genetic variant registry	https://www.ncbi.nlm.nih.gov/clinvar/
FDA	Pharmacogenomic biomarkers in drug labeling	https://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM545881.pdf
GTR: Genetic Testing Resource	Registry of available clinical tests and YouTube tutorials	https://www.ncbi.nlm.nih.gov/gtr/ https://www.youtube.com/playlist?list=PL1C4A2AFF811F6F0B
IGNITE: Implementing GeNomics In practice Network	Consortium investigating barriers to implementation of genetic testing in clinical care	www.ignite-genomics.org
MedGen	Information on genetic disease, clinical characteristics, variants and genetic testing, professional guidelines	https://www.ncbi.nlm.nih.gov/medgen/
NIH/NHGRI: The National Institutes of Health National Human Genome Research Institute	Genetic testing coverage and reimbursement, regulation, human subjects and privacy, informed consent, and legislation	https://www.genome.gov/27527652/genomic-medicine-and-health-care/
NIH/NHGRI: The National Institutes of Health National Human Genome Research Institute	Handbook and toolkit for introductory training of physicians in genomic medicine	https://www.genome.gov/27569865/2017-news-feature-genomics-handbook-provides-customized-education-for-phys

Source	Information provided	Website or reference
OMIM: Online Mendelian Inheritance in Man	Database of genes related to Mendelian disorders	http://omim.org/
PharmGKB: The Pharmacogenomics Knowledgebase	Comprehensive resource that curates knowledge of genetic variation impacting drug response	https://www.pharmgkb.org/
PGRN: The Pharmacogenomics Research Network	Tools to find potentially actionable variants for pharmacogenomics	http://www.pgrn.org http://www.pgrn.org/tools.html

Table 2

Selected drug-gene pairs with a guideline recommendation.

Drug (Clinical use)	Genetic testing indication	Positive genetic test results^	Negative genetic test results^	Evidence for clinical utility	Treatment guidance
Abacavir (1st- line treatment of HIV infection)	Screening to avoid immune-mediated hypersensitivity reactions (occurs in ~6% of pts)	1-2 copies of *HLA-B**57:01	0 copies of *HLA-B**57:01	PREDICT-1: NPV=100%, PPV=47.9%, evidence for cost-effectiveness; recommended by FDA [26,30]	PharmGKB GL[72]; drug contraindicate d for pts w/*HLA-B**57:01
Allopurinol (treatment of gout)	Screening to avoid severe cutaneous adverse reactions	1-2 copies of *HLA-B**58:01	0 copies of *HLA-B**58:01	Significantly increased risk (ORs of 80-580) for pts w/ *HLA-B**58:01 variant[48-53]	PharmGKB GL[73]; drug contraindicate d for pts w/ *HLA-B**58:01
Atazanavir (antiretroviral protease inhibitor)	Screening for drug-related jaundice	Intermed metabolizer: presence of 1 *UGT1A1* decreased-function allele (*6, *28, *37) w/ *UGT1A1**1 (normal function) or *UGT1A1**36 (increased function), 1 copy of rs887829 T allele; poor metabolizer: 2 decreased-function alleles (*UGT1A1**6, *28, *37) or 2 copies of rs887829 T alleles	*UGT1A1**1/*1; *1/*36; *36/*36; rs887829 C/C	AIDS Clinical Trials Group protocol A5257: high likelihood of developing jaundice resulting in atazanavir discontinuation w/ *UGT1A1* poor metabolizers [54,55]	PharmGKB GL[74]
Azathioprine (immunosuppr essant used in solid organ transplant & immunological disorders)	Dose adjustment for variants related to low or deficient drug metabolism	*TPMT* intermed activity (3%-14% of pts): 1 functional allele (*1) + 1 nonfunctional allele (*2, *3A, *3B, *3C, *4); low/ deficient activity (1 in 178-3,736 pts): 2 nonfunctional alleles (*2, *3A, *3B, *3C, *4)	*TPMT**1/*1	Substantial evidence that dose adjustments based on *TPMT* reduce adverse effects w/out compromising desired therapeutic effects [56]	PharmGKB GL[75]
Carbamazepin e (anticonvulsan t, also used in trigeminal neuralgia)	Screening for Steven-Johnson syndrome & toxic epidermal necrolysis	1-2 copies of *HLA-B**15:02	0 copies of *HLA-B**15:02	Significant association of *HLA-B**15:02 genotype in pts w/ Asian ancestry w/ carbamazepine-induced Steven-Johnson syndrome & toxic epidermal necrolysis vs carbamazepine-tolerant pts & healthy controls [34]	PharmGKB GL[76]; use alt drug for pts testing positive if naïve
Clopidogrel (antiplatelet drug)	Screening before percutaneous coronary angioplasty for effectiveness (non-response)	*CYP2C19* ultra-rapid metabolizer (~5%-30% of pts): 2 increased-activity alleles (*17) or 1 functional allele (*1) + 1 increased-activity allele (*17); intermed metabolizer (~18%-45% of pts): 1 functional allele (*1) + 1	*CYP2C19**1/*1	Substantial literature implicating LOF *CYP2C19* alleles in adverse clopidogrel responses, FDA black box warning on drug label [57]; TRITON-TIMI 38: vs noncarriers, pts w/ reduced-function *CYP2C19* allele have HR of 4.79 (1.40-16.37) for death from CV causes, 1.38 (0.94-2.02) for nonfatal MI, 3.93	PharmGKB GL[77]; *CYP2C19* ultra-rapid metabolizer: use standard dose; intermed & poor metabolizer: use alt drug

Drug (Clinical use)	Genetic testing indication	Positive genetic test results^	Negative genetic test results^	Evidence for clinical utility	Treatment guidance
		LOF allele (*2-*8), or 1 LOF allele (*2-*8) + 1 increased-activity allele (*17); poor metabolizer (~2-15% of pts; *4-*8 rarely seen): 2 LOF alleles (*2-*8)		(0.66-23.51) for nonfatal stroke, & 3.09 (1.19-8.00) for stent thrombosis [58]	
Codeine (analgesic)	Screening for efficacy (poor metabolizer, insufficient pain relief) & toxicity (ultra-rapid metabolizer, due to increased metabolism to morphine)	*CYP2D6* ultra-rapid metabolizer (~1-2% of pts): 2+ copies of functional alleles (*1/*1xN, *1/*2xN); intermed metabolizer (~2-11% of pts): 1 reduced & 1 nonfunctional allele (*4/*10, *5/*41); poor metabolizer (~5-10% of pts): nonfunctional alleles (*4/*4, *4/*5, *5/*5, *4/*6)	*CYP2D6* *1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10	Substantial evidence for decreased analgesia in poor metabolizers & severe or life-threatening toxicity following normal doses of codeine in ultrarapid metabolizers [59]	PharmGKB GL[78]
Ivacaftor (cystic fibrosis treatment)	Screening for drug efficacy (non-response)	2 copies of *CFTR* F508del (rs113993960 or rs199826652 genotype del/del)	0-1 copies of *CFTR* F508del; 1-2 copies of the following *CFTR* variants ^^: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, D1270N, G551D	*CFTR* F508del 2 copies: no significant reduction in sweat chloride concentrations, drug provides no clinical & lung function improvement [23]; G551D/G551D or G551D/F508del: improvement of lung function, weight, risk of pulmonary exacerbation, & reduction in sweat chloride concentrations w/ drug use; moderate evidence for improvement w/ 1+ copy of variants in ^^ except G551D	PharmGKB GL[79]; 2 copies of *CFTR* F508del: ivacaftor not recommended ; G551D/G551 D or G551D/F508d el: ivacaftor recommended
Phenytoin (anticonvulsan t)	Screening to avoid cutaneous adverse reactions of Stevens-Johnson syndrome & toxic epidermal necrolysis	1-2 copies of *HLA-B**15:02; *CYP2C9* intermed metabolizer (~8% of pts): *1/*2, *1/*3; *CYP2C9* poor metabolizer (~1% of pts): *2/*2, *3/*3, *2/*3	0 copies of *HLA-B**15:02; *CYP2C9**1/*1	Significantly increased risk of Steven-Johnson syndrome & toxic epidermal necrolysis w/ *HLA-B**15:02 variant in Asian groups (OR, 4.26 [1.93-9.39])[60,61]; phenytoin maintenance doses reduced by 23%-38% in heterozygous pts & by 31-52% in homozygous pts for decreased-function *CYP2C9* alleles[62-64]	PharmGKB GL[80]; *HLA-B**15:02: drug contraindicated for phenytoin-naïve pts
Simvastatin (lipid-lowering drug)	Screening to avoid simvastatin-induced myopathy (myalgias occur in 1-5% of exposed pts)	Intermed function in plasma clearance of simvastatin: 1 copy of decreased-function allele of *SLCO1B1* (*5, *15, *17) or rs4149056 T/C; low function: 2 copies of *SLCO1B1*5, *15, *17* or rs4149056 C/C	Normal function: *SLCO1B1*1a/*1a, *1a/*1b, *1b/*1b* or rs4149056 T/T	RCT (SEARCH) & clinical practice-based cohorts (HPS): ORs for myopathy of 4.5 & 2.6, respectively, per copy of the minor C rs4149056 allele w/ simvastatin (less evidence for other statins); STRENGTH: highest overall effect size of drug discontinuation for any	PharmGKB GL[81]

Drug (Clinical use)	Genetic testing indication	Positive genetic test results^	Negative genetic test results^	Evidence for clinical utility	Treatment guidance
				adverse effect, myalgia, muscle cramping, or elevated serum CK levels >3-fold of ULN for simvastatin (OR 2.8 [1.3-6.0]) compared to atorvastatin (OR 1.6 [0.7-3.7]) or pravastatin (OR 1.06 [0.22-4.8])[65-68]	
Tacrolimus (immunosuppr essant)	Dose adjustments for variants related to enzyme expression	*CYP3A5* extensive metabolizer: **1/*1;* intermed metabolizer: **1/*3*, *1/*6, *1/*7	*CYP3A5* poor metabolizer: *3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7	Strong evidence based on more than 50 studies for use of tacrolimus in kidney, heart, lung, HSCT, & liver Tx pts where the donor & recipient genotypes are identical; [69] ongoing clinical trials: ClinicalTrials.gov	PharmGKB GL[82]
Warfarin (oral anticoagulant)	Dose adjustment & efficacy based on metabolism (*CYP2C9*) & sensitivity (*VKORC1*)	Non-African ancestry: *CYP2C9**2/*3, *3/*3 (poor metabolizer) or both increased sensitivity (*VKORC1* 1639 A/A or A/G) & *CYP2C9* poor metabolizer; African ancestry: *CYP2C9**5 or *6 or *8 or *11, rs12777823 A/G or A/A, *CYP4F2**3	*CYP2C9**1 + 0 copies of other alleles listed as positive test; 0 copies of *CYP2C9* rs12777823 A allele (only in African ancestry); 0 copies of *VKORC1* 1639 A allele; 0 copies of *CYP4F2**3 ^^^	EU-PACT & COAG trials for genotype-guided dose adjustments; GIFT trial showed the effectiveness and safety of genotyped-guided dosing for VTE & major bleeding (27% reduction) [21,70,71]	PharmGKB GL[83]

Footnote: Based on information from the Clinical Pharmacogenetics Implementation Consortium guidelines (CPIC) and PharmGKB. The most updated version of these guidelines can be found at https://cpicpgx.org/guidelines/.

Alt, alternative; NPV, negative predictive value; PPV. Positive predictive value; COAG, Clarification of Optimal Anticoagulation Through Genetics; CV, cardiovascular; HPS, Heart Protection Study; HSCT, hematopoietic stem cell transplant; intermed, intermediate; MI, myocardial infarction; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; STRENGTH, Statin Response Examined by Genetic Haplotype Markers; EU-PACT, European Pharmacogenetics of Anticoagulant Therapy; PREDICT-1, Prospective Randomized Evaluation of DNA Screening in a Clinical Trial; TRITON-TIMI, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction; LOF, loss of function; RCT, randomized controlled trial; Tx, transplant; ULN, upper limit of normal.

^ Laboratory reporting of genetic variants varies; a positive result would be one guiding treatment modifications, while a negative result would one with no modification in drug regimen needed.

^^ SNP numbers are as follows for the following amino acid changes: E56K (rs397508256), P67L (rs368505753), R74W (rs115545701), D110E (rs397508537), D110H (rs113993958), R117C (rs77834169), E193K (rs397508759), L206W (rs121908752), R347H (rs77932196), R352Q (rs121908753), A455E (rs74551128), D579G (rs397508288), S945L (rs397508442), S977F (rs141033578), F1052V (rs150212784), K1060T (rs397508513), A1067T (rs121909020), G1069R (rs200321110), R1070Q (rs78769542), R1070W (rs202179988), F1074L (rs186045772), D1152H (rs75541969), D1270N (rs11971167), G551D (rs75527207)

^^^ additional variants need to be genotyped in those of African ancestry