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Clinical and Public Health Implications of Emerging Genetic Technologies

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Summary

The clinical utility of many emerging genetic technologies has yet to be established. For many new genetic tests, no practice guidelines are available to help clinicians decide when and how to use them in practice. The clinical and public health implications of new genetic technologies are easiest to evaluate when these tests are compared with other genetic tests, including those already well established in clinical practice. Genetic tests can be divided into different categories based on their intent as follows: (1) to establish a diagnosis (genetic diagnostic tests), (2) to classify disease processes to assist management (gene expression profiling), (3) to predict drug response or side effects (pharmacogenomic tests), and (4) to predict susceptibility to disease (genetic susceptibility testing). As new genetic tests emerge, their translation into practice will depend on their performance based on laboratory standards, but also on their ability to enhance prevention or assist clinicians in diagnosing and treating patients. This article reviews the clinical and public health implications of different types of genetic tests, the evaluation of genetic tests from a public health perspective, and the need for partnership to achieve the potential for benefit of new genetic technologies.

Keywords

Genetic testing; public health genetics; health technology assessment; translation; clinical utility

Nephrologists and other clinicians are confronted with a host of emerging genetic tests, available for a wide range of clinical purposes. Often evidence about clinical utility is difficult to find or lacking, and relatively few practice guidelines are yet available.¹ Physicians legitimately are concerned about using genetic tests in the absence of robust data about the appropriate use of test results in patient management: in qualitative interviews with 60 primary care providers, for example, the most frequently mentioned barrier to integration of genetic tests in clinical practice was lack of information about clinical utility (60%).²

Uncertainties are particularly high for tests that identify genetic susceptibility to common diseases such as diabetes and coronary heart disease. A growing number of such tests are made

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possible by the success of genome-wide associations studies (GWAS),³ and the use of genetic testing for this purpose is perceived as one of the major potential benefits of the Human Genome Project.⁴ Some experts anticipate that “personalized genomics”—tests that identify multiple different susceptibilities in a single assay—could provide a new approach to disease prevention and early versions of this kind of testing already are available directly to the consumer.^{5,6}

The clinical and public health implications of personalized genomics are easiest to evaluate when these tests are placed in context with other genetic tests, including those already well established in clinical practice. Genetic tests can be divided into different categories based on their intent: to establish a diagnosis (genetic diagnostic tests), to classify disease processes to assist management (gene expression profiling), to predict drug response or side effects (pharmacogenomic tests), and to predict susceptibility to disease (genetic susceptibility testing) (Table 1). Many genetic tests also can be distinguished by their use in screening or in the management of a clinical problem (Table 2). As new genetic tests emerge, their translation into practice will depend on their performance based on laboratory standards, but also on their ability to enhance prevention or assist clinicians in diagnosing and treating patients.

IMPLICATIONS OF DIFFERENT TYPES OF GENETIC TESTS

Genetic Diagnostic Tests

Many genetic disorders are diagnosed using clinical criteria. However, genetic testing increasingly is being used to confirm or assist in making a clinical diagnosis. Testing also may help to inform family members about their risk, and sometimes can provide information for prognosis or patient management. Genetic diagnostic tests typically are ordered by genetics professionals after an evaluation of the patient’s physical examination and medical and family history. Examples relevant to nephrology include conditions such as Fabry disease (an X-linked recessive disorder that includes renal failure), von Hippel-Lindau disease (an autosomal-dominant disorder that includes renal cell carcinoma), and the collagen-IV-related nephropathies (Alport syndrome and thin basement membrane nephropathy), which occur in X-linked, autosomal-recessive, and autosomal-dominant forms.

One of the most common genetic disorders of the kidney, autosomal-dominant polycystic kidney disease (ADPKD), illustrates the potential uses of genetic diagnostic tests. ADPKD is characterized by the presence of bilateral renal cysts, cysts in other organs (liver, pancreas, and so forth), and extrarenal manifestations (intracranial aneurysms, dilation of the aortic root, and so forth), in the absence of other causes of cystic renal diseases. The diagnosis of ADPKD is made in individuals with a family history based on the presence of a minimal number of renal cysts for a given age (2 unilateral or bilateral cysts if <30 years old; 2 cysts in each kidney if 30–59 years old; or 4 cysts in each kidney if ≥60 years old).⁷ The sensitivity of these criteria is estimated at 100% for individuals older than 30 years of age.⁸

ADPKD is caused by mutations in two genes: PKD1, which accounts for approximately 85% of affected individuals, and PKD2, which accounts for the remaining 15% of cases. Mutation detection rates in PKD1 and PKD2 by sequencing are 88% and 92%, respectively.^{9,10} A small number of cases (<1% to 4%) are caused by partial or whole-gene deletions or duplications.¹⁰ About 10% of cases of ADPKD are thought to be caused by de novo mutations: in this situation, the affected person has no family history and work-up of parents and siblings is normal. However, the affected person’s children are at 50% risk to inherit the condition.

With highly sensitive clinical criteria for diagnosis, what information can genetic testing for ADPKD provide for the patient and his management? First, it can help in the diagnosis of younger adults at risk and individuals with no known family history. In a family with a known history of ADPKD, genetic testing can confirm the presence of the familial mutation in

asymptomatic adults or adults with renal cysts but who do not quite yet meet the clinical criteria. In affected individuals, genetic testing can provide an earlier diagnosis, earlier management of complications, and establishment of adequate follow-up evaluation and surveillance. In unaffected individuals, genetic testing can help reduce anxiety and unnecessary follow-up evaluation for those who have not inherited the familial mutation. However, predictive genetic testing in individuals who have no cysts on ultrasound should be performed only after appropriate counseling and informed consent. Counseling should address potential impacts of negative or positive results, including issues of insurability and employability.

Predictive genetic testing may be particularly important when a definite diagnosis is required, as when a young adult is a potential kidney donor for an affected relative. In this case, predictive genetic testing can help determine whether the seemingly unaffected individual has inherited the familial ADPKD mutation or not, and therefore whether he/she would be a suitable donor. Because disease manifestations usually are not present during childhood and no preventive treatments are available, predictive testing of children is not recommended.

There is significant intrafamilial phenotypic variability in the severity of renal disease and in the range of extrarenal manifestations, suggesting that genetic and environmental modifiers influence disease presentation and course.¹¹ Nevertheless, there are correlations between the genotype (the particular mutation or gene variation found in a given individual) and phenotype (the clinical signs and symptoms shown by that individual). For example, mutations in the 5' region of the PKD1 gene are associated with more severely affected renal function,¹² and patients with these mutations are more likely to develop intracranial aneurysms.¹³

Gene Expression Profiling

Gene expression profiling represents a new genetic testing strategy. This testing approach is used to measure expression of genes in specific disease states, caused either by abnormal transcription or acquired genetic change, as opposed to inherited genetic variants. Gene expression profiling is used to differentiate between different stages of a disease and hopefully provide noninvasive tools for early diagnosis of disease progression. It has been used mainly in oncology to stage tumors, but increasingly is being studied in other chronic conditions.

For example, microarray technology is being used to look for gene expression profiles that indicate early signs of rejection in organ transplant patients.¹⁴ Recent findings suggest that using expression of specific markers could help identify chronic rejection early. In one study, expression of three proteins could explain 28% of the variability of creatinine at 1 year posttransplant, compared with 14% by histology alone (CADI score).¹⁵ As more proteins are added to the panel, results might become more accurate but the analysis becomes increasingly more complex because the relationship between the markers needs to be taken into account. Similar efforts are being made to characterize diabetic nephropathy and to identify markers for disease progression.¹⁶

This technology is not yet used in clinical settings for these purposes, but already is used to guide management of patients with breast cancer.¹⁷ The level of evidence needed to support the use of these tools in clinical practice is a matter of debate.¹⁸ There will be a need for prospective evaluation of the impact of the use of these gene expression profiles on patient management and ultimately patient outcomes to guide their integration in practice.

Pharmacogenomics

Pharmacogenomics represents one of the most promising new clinical applications of genomic research. Testing for gene variants associated with drug response has the potential to improve both the safety and the efficacy of drug treatment. In the most widely anticipated use of

pharmacogenomics, testing would occur before prescribing commonly used drugs to ensure that the appropriate drug or appropriate dosage is chosen based on the patient's likelihood of adverse reactions or response. In contrast to genetic diagnostic testing, tests most likely will be ordered by nongenetics professionals, in the absence of genetic counseling. Practice guidelines, and accepted standards for defining good test use, will therefore be an important consideration as different clinical specialties integrate this testing paradigm.

The ability to use pharmacogenetic testing to predict required dosage to maximize efficacy and/or minimize side effects is particularly well suited for drugs with a narrow therapeutic index, such as immunosuppressive drugs. Underdosing of immunosuppressive agents can lead to rejection of a transplanted kidney, whereas overdosing can lead to serious side effects, including nephrotoxicity.¹⁹ There is a poor correlation between dose and blood concentration. The heterogeneity of individual response results in difficulties in achieving target blood concentrations early after transplantation, which are important for reducing the rate of immunologic rejection. The main determinant of heterogeneity in dose requirements is absorption and metabolism of the drug into its active form. It is hoped that genotyping patients for genes involved in absorption and metabolism of these drugs might have the potential to aid the establishment of optimal dosage regimens for transplant patients. For example, genetic polymorphisms in *CYP3A5* and *MDR1* genes influence plasma levels of immunosuppressive drugs such as tacrolimus and cyclosporine in renal transplant patients.²⁰ Renal transplant patients receiving tacrolimus who carried the 1236C>T variant or the 2677G>T variant in the *MDR1* gene had drug concentrations, respectively, 44% and 45% higher than noncarriers. Renal transplant patients receiving cyclosporine who carried the 22915A>C variant had drug concentrations 52% higher than noncarriers. This suggests that individuals who carry these variants could receive lower doses of these drugs to reach therapeutic concentrations.

In other cases, the added value of pharmacogenetic testing is to identify individuals at risk of serious side effects. Trade-offs between risks of the drug and risks of alternative therapeutic approaches require careful consideration. For example, mutation A1555G in the 12S ribosomal RNA mitochondrial gene is associated with an increased risk of aminoglycoside-induced deafness. Aminoglycosides are commonly used antibiotics for serious infections, including acute pyelonephritis. It is estimated that practically all individuals with the predisposing variant develop deafness if exposed to aminoglycosides. If unexposed to aminoglycosides, the risk of hearing loss by age 30 is about 40%.²¹ In populations that are likely to receive aminoglycosides, such as cystic fibrosis patients, screening for the A1555G mutation has been suggested. Avoidance of aminoglycosides in patients carrying this mutation will decrease the incidence of deafness but could lead to worse outcomes in patient survival if alternate therapies are not as effective as aminoglycosides at treating infections.²² As long as alternative treatments are not at least as effective as aminoglycosides, widespread screening likely will not be recommended.

The level of evidence required to justify routine use of pharmacogenomic tests is not yet established; in particular, there is controversy concerning the need for randomized controlled trials to assess the outcomes of pharmacogenomically assisted prescribing before its integration into practice. Once a specific pharmacogenetic test is determined to be useful, clinicians will need to be educated in how to appropriately prescribe it and how to interpret and apply its results.

An important question in the evaluation of pharmacogenomic testing is whether it poses significant personal or social risks. Testing is focused on informing drug prescribing, but many pharmacogenomic tests provide ancillary information, defined as information unrelated to drug response, such as predisposition to diseases for which the individual is not currently seeking treatment or does not manifest symptoms, or prognostic information that is not informative for

treatment.²³ The implications of this information for informed consent or appropriate use of pharmacogenomic tests is not yet resolved. Conceivably, some pharmacogenomic tests could raise sufficient risks to make genetic counseling a consideration.²⁴

Genetic Susceptibility Testing and Personal Genomics

GWAS have identified many genes or gene variants as potentially associated with a higher risk of a given disease. This is true for a wide variety of diseases. Recent examples include hypertension and kidney stones.^{25,26} Others examine the genetic susceptibility of developing disease complications such as diabetic nephropathy in individuals with diabetes.²⁷ These findings have yet to be used to develop tests for clinical practice, but there is a hope that better understanding of the genetic factors involved can help identify individuals at high risk of developing disease that could benefit from early intervention and surveillance. Other genetic susceptibility tests related to common disease risks are now available for clinical use (eg, diagnostic tests to identify risks for cancer, glaucoma, and cardiac diseases offered by deCODE Genetics).²⁸

Similar to the other types of tests discussed earlier, genetic susceptibility testing raises questions regarding evaluation and appropriate use. When is genetic risk information useful and when is it harmful? Who decides? In light of the large volume of risk information that will flow from genomic research, these questions are critically important for health care policy. We are still ill-equipped to interpret most of these test results, especially because we still do not know all of the genetic factors involved in common conditions, how they interact with nongenetic risks, and how they combine to predispose or protect individuals from disease.

Consideration of genetic susceptibility testing leads to fundamental inquiries about the purpose of health care, incorporating how broadly *health* and *health outcomes* should be defined, and the limits that should be set on the use of health care resources. Genetic susceptibility testing also poses questions about delivery of care, including the degree to which current systems of primary or specialty care can be better focused on prevention. To the extent that prevention can be made a central focus of health care, rigorous questions will need to be asked about the value added by knowledge of genetic risk: for example, if the health care system already were maximizing efforts to promote healthy diet, how would knowledge of genetic risk for diabetes or coronary artery disease assist patients or providers?

In the most expansive vision of this type of genetic testing, often termed *personalized genomics*, tests for a broad array of susceptibilities and pharmacogenomic variants would be combined into a single test, and routinely assessed to guide both prevention and clinical care. Some experts envision moving from comprehensive panel tests to a full genome sequence as the basis for routine health care.²⁹ Many questions arise, for example, how to validate the large amounts of genomic risk data that will be forthcoming from such tests, and how to manage the inevitable false-positive and false-negative findings. Storage and retrieval of genetic susceptibility information also poses challenges. The information will need to be readily accessible in all places where a patient receives health care if it is to be maximally effective. At the same time, appropriate privacy protection will be essential.

Although these tests provide information with potential implications not only for the patient being tested but also for his/her family members, such tests are anticipated to require genetic counseling. However, practice standards, including the evidence needed to justify test use, are not yet established. The role of genetics professionals are not yet established either, either in setting practice standards or in assisting other clinicians by means of educational efforts, consultation, or counseling.

EVALUATING GENETIC TESTS: IMPLICATIONS FOR PERSONAL GENOMICS

The performance of a genetic test is not based only on its analytic and clinical validity, that is, whether the test identifies the variant correctly and is able to predict the disease of interest.³⁰ Its performance in practice also rests on its clinical utility, referring to the likelihood that a test will lead to improved health outcomes. Clinical utility requires evaluation of the benefits and risks associated with testing, including related clinical interventions, their effectiveness, and their social consequences.³¹ Improved health outcomes will occur only if effective preventive strategies, treatments, or other actions are available for patients found to be at higher risk based on the genetic test result and that no net harm occurs as a result of either positive or negative test results.³²

The translational research involved in developing a gene–disease association into a test for health care use has been described in multiple steps,^{33–36} including foundational research (T1), health application (T2), health practice (T3), and health impact (T4). The first step involves the basic science leading to the development of a candidate health application, such as a genetic test, meant to guide clinical evaluation or treatment decisions (T1). During the second step, clinical research is undertaken to evaluate the test (T2), followed by introduction of the test into practice (T3), and evaluation of outcomes (T4) (Fig. 1). Each of these steps requires research to ensure that the intervention can be applied reliably, is effective in achieving the intended clinical outcomes, is available to patients, and used appropriately in practice. However, most current studies focus on the identification of genetic causes for disease and early translational research: the impact of the integration of genetic tests in routine clinical practice on patient health and quality of life (ie, its clinical utility) rarely is measured.³³

As a result, for many genetic risk factors, there is no clear evidence of the effectiveness of interventions in individuals at risk.³⁷ Hypotheses about test benefit may be based on inferences from observational data. Research findings need to be replicated and validated before tests are developed for clinical use.³⁰ Furthermore, the use of the genetic test in daily practice likely is different from its use in the context of controlled trials, even when these are available. Genetic tests destined for wide population applications can be evaluated using methods developed by the Evaluation of Genomic Applications in Prevention and Practice working group.³⁸ Yet, the identification of genetic risk factors (or genetic susceptibility variants) has in some cases rapidly led to the development of genetic tests for clinical use.³⁷

In theory, the integration of genetic tests into practice would be facilitated by the development and dissemination of evidence-based guidelines.³³ In reality, clinical practice guidelines for genetic tests still are uncommon, and most of the existing guidelines were issued once tests already were used in clinical practice. The paucity of clinical practice guidelines is largely owing to the lack of strong evidence of clinical utility. In addition, physician adherence is variable even when clinical practice guidelines are available.³⁹ Vague, nonspecific, or controversial recommendations are less likely to be followed, as are recommendations requiring a change in routine practice.⁴⁰ Their applicability to common clinical situations and to different types of patients also influences their uptake.^{39,41}

ACHIEVING BENEFIT: THE NEED FOR PARTNERSHIP

As evidence emerges to document the clinical utility of new genetic tests, that is, the likelihood that a test will lead to improved outcomes,³¹ clinicians and health care decision makers will need to develop practice standards to ensure appropriate use. In the case of genetic diagnostic tests, the confirmation of an inherited disorder often provides helpful prognostic information and may lead to specific surveillance of complications or treatments. These tests are likely to remain in the hands of genetic professionals and specialists familiar with specific genetic conditions.

In the other types of tests discussed earlier, clinical utility is not as straightforward, and will require the same critical review and development of evidence-based practice standards that clinicians look for with other medical innovations. Gene expression profiling, for example, may involve substantial difficulties in interpretation and application at the individual patient level, as shown with available evidence on OncotypeDx profiles used to guide management of patients with breast cancer.¹⁸ Pharmacogenomic testing will be helpful only if the identifications of variants in a patient can improve achievement of therapeutic drug levels or avoidance of side effects. If the occurrence of side effects is not related to drug level or if drug dosage is predicted only partially by pharmacogenomic information, the end result might not be better than close clinical monitoring of drug levels. Such difficulties have been observed with pharmacogenomic testing for warfarin dosage.⁴² Genetic susceptibility testing currently is limited by our ability to identify only a fraction of the genetic factors involved in the development of most common diseases and by the low relative risks associated with most risk variants. Overuse of this risk information in decisions about surveillance and treatment of individuals considered to be at risk could lead to iatrogenic complications or side effects in individuals who would never have developed the disease. The use of susceptibility testing in the setting of disease management, for example, identifying diabetics at increased risk for nephropathy, therefore may be less problematic than widespread screening of healthy individuals. All of these concerns emphasize the need for adequate evaluation of new genetic tests and sufficient evidence to support their use in practice. They also raise questions about appropriate strategies for health care delivery.

Until recently, clinical geneticists were the largest users of genetic tests and technologies. However, emerging tests are targeted increasingly toward patients who will not be seen by clinical geneticists. Genetics professionals often may have expertise relevant for test interpretation or pretest or posttest counseling, but the small number of clinical geneticists and genetic counselors in practice will limit their ability to participate in the care associated with an expanding menu of genetic tests. An important role emerging for geneticists is in training other specialists about the use and interpretation of genetic tests to enable them to take on the diagnosis and treatment of many patients with genetic disorders, and to incorporate genetics increasingly in their practice. Clinical geneticists likely will become consultants for complex cases, but they will need to work in partnership with other specialties to define the appropriate boundaries of practice as more genetic health applications emerge. Clinical geneticists are not the first to struggle with this dilemma,⁴³ which has been compared with the one faced by infectious disease specialists in the past century. As new tests and antibiotic treatments became available, infectious disease specialists started to focus on the diagnosis of complex cases and less common disorders, as well as the use of the newest therapies, while common diseases and their treatments were dealt with by other specialists.⁴⁴ The advent of new technologies led to a redefinition of the specialists' role, not their disappearance.

Nephrologists and other specialists can offer important and needed expertise, in partnership with genetics professionals, in determining the appropriate uses of genetic testing within their practice, as well as indications for referral to a clinical geneticist. Educational materials based on such partnership are needed.⁴⁵ In addition, current reimbursement practices often do not cover the costs associated with the provision of genetic counseling and related genetic services,⁴⁶ and may be difficult to access in rural areas. Some emerging uses of genetics testing and technology are integrated readily into existing health care whereas others may require specific efforts to define appropriate use and the role of genetics professionals. Telemedicine, reimbursement for virtual consultation, and other innovative approaches may be necessary to ensure the optimal delivery of some new services.

CONCLUSIONS

Emerging genetic knowledge is increasing our understanding of disease processes in many areas. This new knowledge will follow a translational pathway that will take it from the laboratory to the bedside in the hope that it eventually will lead to improved outcomes for patients. Along this pathway, each step in the development of new tests and their introduction into clinical care needs to be evaluated carefully to ensure that the benefits for patients outweigh the harms and that clinicians are well equipped to use and interpret the test results.⁴⁷ In the future, genetic diagnostic tests, gene expression profiles, pharmacogenetic tests, and genetic susceptibility tests hopefully will guide nephrologists in the management of patients with a variety of kidney-related conditions. Determining the practice standards of the future will require a partnership between nephrologists and geneticists, and may require innovative approaches to practice delivery.

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Figure 1.
Translation of gene discoveries into health care applications.

Table 1

Example of Genetic Tests Based on Test Purpose

Test Purpose	Example
Genetic diagnostic test	Testing to confirm the diagnosis of autosomal polycystic kidney disease
Gene expression profiling	Potential strategy to identify early signs of organ rejection
Pharmacogenomic test	Testing to identify individuals with CYP3A5 variants associated with a higher risk of complications from immunosuppressive drugs (tacrolimus, cyclosporine)
Genetic susceptibility test	Testing to identify individuals at increased risk of diabetes, hypertension, and/or multiple other disease risks

Table 2

Examples of the Potential Use of a Genetic Test in Individual Clinical Settings Versus Screening Settings

Test Purpose	Clinical Management	Screening
Genetic diagnostic test	Diagnosis of congenital adrenal hyperplasia in patient with suggestive symptoms or family history	Newborn screening for congenital adrenal hyperplasia
Pharmacogenetic test	CYP3A5 testing in renal transplant patient before treatment with tacrolimus	Pharmacogenomic profiling (including CYP3A5 testing) as part of routine health care, with data stored for use with all drug prescribing
Genetic susceptibility test	Testing for genetic susceptibility to diabetes in a person with a high body mass index	Routine screening of healthy adults to identify those at increased risk