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Future translational applications from the contemporary genomics era: a scientific statement from the American Heart Association.

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Future Translational Applications From the Contemporary Genomics Era:

A Scientific Statement From the American Heart Association

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Abstract

The field of genetics and genomics has advanced considerably with the achievement of recent milestones encompassing the identification of many loci for cardiovascular disease and variable drug responses. Despite this achievement, a gap exists in the understanding and advancement to meaningful translation that directly affects disease prevention and clinical care. The purpose of this scientific statement is to address the gap between genetic discoveries and their practical application to cardiovascular clinical care. In brief, this scientific statement assesses the current timeline for effective translation of basic discoveries to clinical advances, highlighting past successes. Current discoveries in the area of genetics and genomics are covered next, followed by future expectations, tools, and competencies for achieving the goal of improving clinical care.

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[*] Modest.

[†] Significant.

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Keywords

AHA Scientific Statements; adrenergic beta-antagonists; DNA; genetics; genome-wide association study; HapMap Project; Human Genome Project; PCSK9 protein; mouse; polymorphism; single nucleotide

With the completion of the Human Genome Project (HGP) in 2000 and the International HapMap Project in 2003, genetics research focused on complex traits has exploded. The success of genome-wide association studies (GWASs) has identified many new single-nucleotide polymorphisms (SNPs) for common, complex traits and diseases (http://www.genome.gov/gwastudies). In the area of cardiovascular disease (CVD), loci have been identified for myocardial infarction (MI)[1] and CVD risk factors, including blood pressure,[2] lipids,[3] obesity,[4,5] and diabetes mellitus.[6,7]

At the 10-year anniversary of the completion of the HGP, an article appeared in the *New York Times*. This article, "A Decade Later, Genetic Map Yields Few New Cures," stated that "despite early promise, diseases' roots prove hard to find."[8] This article highlighted the lack of meaningful clinical implications derived from the HGP. For MI, each successful GWAS and its newly discovered SNP associations have fallen short in their ability to predict incident MI.[9] This may be attributable to the very small effect sizes of the newly discovered variants in their association with MI. In contrast, these new discoveries have provided novel insights into unsuspected mechanisms for disease that may serve as potential therapeutic targets. GWASs have landed on many known drug targets,[10] and the probability is high that this will continue. Of all clinical fields, genetics in cancer diagnosis and treatment has been quite successful.[11,12]

The notion of slow translation to clinical application is not new. The concept of the "valley of death" broadly applies to barriers in translating discoveries and the chasm that exists between the discovery of new potential therapeutic agents and their ultimate clinical utility.[13] Much has been written about this concept and the need to restructure relationships between academia, government, and industry, as well as the need for adequate support to facilitate translation.[10,13,14] Scientists studying mechanisms of disease are aware of the high costs and the time necessary to carry out experiments to translate how newly identified mutations may alter phenotypes. New technologies, strategies, and programs designed to expedite the translation of genetics and genomics are waiting to be used. Although new strategies exist, many academic laboratories may not be well versed in or even aware of these methodologies. Moreover, these techniques require time, experience, and education from investigators and laboratory staff. How this learning process can best be facilitated is unclear. The field of CVD has much to gain from these strategies, given that CVD is currently the leading cause of death in the United States.[15]

Thus, the purpose of this scientific statement is to detail steps currently used to realize important clinical translation from genetic data and to provide a look into the future at steps that may prove more effective. This scientific statement discusses past successes, emerging science and applications, and future directions to ensure effective translational activities and applications. Included in this scientific statement are 5 tables and 2 figures. The 5 tables

outline examples of genomic discoveries that have translated into currently used clinical therapies, emerging clinical tools, steps to facilitate genomic and genetic discovery, and the phases of clinical trials. The figures depict the timeline of tools that were established to enable rapid discovery in the area of genetics and genomics and a flowchart for the steps, timeline, and costs from SNP identification to achieving clinical utility. Through this presentation, we hope to achieve transparent expectations for the public and for the medical and scientific communities in the steps, resources, and time that are necessary to achieve clinical advances from recent genetic discoveries.

The HGP and Extensions of This Project

Many advances in the field have been supported by federal investment and infrastructure support (HGP, HapMap, 1000 Genomes, Encyclopedia of DNA Elements [ENCODE]). The HGP was initiated in 1990 as an international research program to determine the DNA sequence of the human genome and to identify the unknown number of genes that encoded the genetic diversity of the human population (Figure 1 gives the timeline of major recent genetics milestones in population genetics). From the initial draft sequence of the human genome, a next-generation map was needed to uncover common (frequency of at least 5%) genetic variants, or SNPs, that describe the fine-structure architecture of the genome in multiple human populations. The National Human Genome Research Institute launched this project, the International HapMap Project, in 2002.

The 1000 Genomes Project (www.1000genomes.org) was launched in 2008 and represents an international research effort to establish an initial catalog of human genetic variation across ethnically diverse populations. The result is a sequence repository and a refined human genome map to be used to identify and characterize disease-causing genes.[16,17] ENCODE (www.genome.gov/10005107) represents a research consortium established by the National Human Genome Research Institute in 2003 to characterize the functional elements in the human genome, to determine their tissue distribution, and to assess how variation in the DNA sequence may affect gene function and regulation. Initial results of the project were released in September 2012 in a series of reports.[18–20]

Ongoing Promises and Public Expectations of the HGP

The HGP has provided tangible benefits for investigators who can begin to define the biological function and pathophysiology of the many newly discovered variants. A limitation of translating the promise of the HGP to molecular medicine has been not knowing which variants are disease causing and which are innocent bystanders. In GWASs, it is likely that fewer than one third of disease-associated SNP variants are within or nearby the portion of the genome (ie, exons) that are responsible for protein-coding changes.[16] The availability and falling costs of whole-genome sequencing are important factors accelerating this effort.

A public perception is that the knowledge of the genome can be translated quickly into advances in medicine, leading to improvements in personalized prediction, prevention, and treatment. Although some practical results emerged quickly in genes identified as primary risk factors for disease, the understanding of how variation in a gene contributes to disease risk requires substantial research. The next section highlights a few past successes in familial

hypercholesterolemia, cancer treatment, and cystic fibrosis to provide insight into what future clinical applications may arise from newly discovered genetic findings. This section is not intended to be a comprehensive overview of successful translation of genomics findings. Table 1 provides an overview of these key areas.

Past Successes of Genetic Findings

Familial Hypercholesterolemia and Low-Density Lipoprotein Cholesterol Lowering

The introduction of the first HMG CoA reductase inhibitor, or statin, into clinical practice in the United States in 1987 transformed the treatment of patients with elevated cholesterol levels and altered the ability of physicians to reduce the risk of future coronary artery disease events in patients with hyperlipidemia. Building on 2 decades of basic biochemistry that had established the critical role of the enzyme HMG CoA reductase as the rate-limiting step in cholesterol biosynthesis, Endo and colleagues[26–30] published evidence describing the ability of 2 fungal metabolites to inhibit that enzyme in 1976. This work, in combination with the human genetic and cell biological studies of Nobel laureates Joseph Goldstein and Michael Brown[21,22] that established a role for the low-density lipoprotein (LDL) receptor in regulating cellular HMG CoA reductase activity, provided both a means for lowering cellular cholesterol levels and a mechanistic understanding of the pathways by which statin inhibition of the reductase would then lead to improvements in serum cholesterol. Together, these data emboldened pharmaceutical companies to rapidly advance statin drugs into the clinic in the early to mid-1980s. The advent of safe and effective statins then provided clinical investigators the tool needed to establish that lowering serum cholesterol with the use of these drugs could substantially reduce coronary heart disease events and near-term mortality rates in hypercholesterolemic patients.[23] It is important to realize that the effect size of any given identified genetic signal does not predict the ultimate clinical yield of intervening in that pathway. For example, in a GWAS of LDL cholesterol, the risk variant in HMG CoA reductase, the limiting enzyme of cholesterol synthesis and the drug target of statins, was associated with variability in LDL cholesterol of 2.3 mg/dL per copy of the minor allele.[31] Although this effect is indeed small, intervening in LDL metabolism can reduce LDL levels by up to 60% and reduce the risk of CVD, underscoring how a small genetic effect size may not necessarily translate to limited therapeutic effectiveness.

Imatinib, a Tyrosine Kinase Inhibitor, for the Treatment of Chronic Myelogenous Leukemia

Genomic studies have advanced care for cancer patients. The revolution in target-based therapeutics is highlighted by successful bench-to-bedside translation across diverse specialties. Notably in oncology, cytotoxic chemotherapy is complemented by rational drug design exemplified by kinase inhibitors.[32] Constitutively activated tyrosine kinases in disease promote tumor proliferation and survival but are effectively neutralized by small-molecule tyrosine kinase inhibitors. Tyrosine kinase inhibitors differ in the spectrum of targeted kinases, pharmacokinetic properties, and toxicology yet share selectivity for aberrant tyrosine kinases and spare healthy cells.[32] The prognosis of chronic myelogenous leukemia has been transformed by specific tyrosine kinase inhibitor regimens. The hallmark of chronic myelogenous leukemia is a Philadelphia chromosome, which is now understood to represent a translocation between chromosomes 9 and 21. This translocation generates a

BCR-ABL fusion oncogene, which translates into an active tyrosine kinase onco-protein.[33] Tyrosine kinase inhibitors improve survival up to 90% by exploiting the presence of the abnormally expressed oncoprotein. Tyrosine kinase inhibition fails in some patients or patients become resistant to therapy. This observation has led to the development of second- and third-generation tyrosine kinase inhibitors.[34] Tyrosine kinase inhibitors are used in multiple cancers, notably melanoma and certain forms of lung and breast cancer.[35–38]

Success in Cystic Fibrosis

Structural insights into channelopathies have been translated into small-molecule approaches to reconstitute chloride-channel function in cystic fibrosis, an inherited disorder caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR).[39] Ivacaftor, a small-molecule potentiator of CFTR, was approved for treatment of patients with cystic fibrosis who harbor a G551D mutation in the *CFTR* gene. This mutation impairs the ability of CFTR at the cell surface to open.[24] High-throughput membrane potential assays were designed to identify CFTR potentiators and led to the development of ivacaftor. This drug improves chloride transport by potentiating the open probability of the G551D-CFTR mutated channel. Beyond allele-specific therapies, drugs in development target whole functional classes of CFTR mutations. For example, the most common CFTR mutation, resulting in ΔF508, opens appropriately but does not traffic normally to the cell surface; small molecules that increase surface expression are in development.

Taken together, established successes in these key areas highlight how discoveries from genetics and genomics have already been translated effectively into clinical therapeutics. The next section briefly outlines emerging areas of science.

Emerging Science

Emerging areas of scientific research include metabolomics, proteomics, nutrigenomics, microbiomics, epigenetics, cloning, induced pluripotent stem cell (iPSC) organization into “organoids,” genetic editing called CRISPR (clustered regularly interspaced short palindromic repeats), small RNAs, and splicing. This American Heart Association scientific statement does not focus specifically on examples from these emerging areas of science.

Another important area of emerging science revolves around race/ethnicity, genetic differences, and vascular phenotypes. An important example is end-stage renal disease in blacks, a group disproportionately affected.[40] A haplotype on 22q12 was identified in association with end-stage renal disease in blacks but not whites. This region was associated with 2- to 4-fold increased risk of end-stage renal disease in blacks and explains the majority of increased end-stage renal disease risk between blacks and whites.[41] Later identified as the *APOL1* gene,[42] the presence of this mutation is unrelated to the degree of blood pressure control in terms of kidney disease progression.[43] These findings highlight how genetic discoveries can provide an underlying biological basis for disease disparities and, in particular, can provide a new pathway for translational efforts.

Effectiveness of Translation to the Clinic

Four areas that have translated or are likely to translate into the clinic include CVD risk prediction, pharmacogenomics, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and clinical actionability of genetic mutations. A very important area that is not covered in this scientific statement is prenatal and reproductive counseling. An overview is presented in Table 2.

Cardiovascular Risk Prediction

Risk prediction is used for decisions about preventive strategies in clinical practice. Risk algorithms for coronary heart disease predict future CVD risk with modifiable CVD risk factors and are embedded in treatment guidelines.[57] With the recent completion of large-scale GWASs, genetic risk scores that incorporate major SNPs for CVD or its risk factors have been constructed and tested for use in the prediction of future CVD. Most studies report only a modest increased genetic risk for CVD outcomes associated with genetic variants, and the incremental contribution to risk discrimination with clinical risk scores alone is small. A consensus is needed for statistical metrics to properly assess the incremental value of the genetic risk score in clinical practice. One set of metrics proposed for the assessment of novel markers in general, but not specifically for genetic markers, includes discrimination and risk reclassification.[58]

A limited number of prospective studies of genetic risk score have evaluated the metrics for assessing incremental benefits of the genetic risk score for coronary heart disease/MI over and above currently measured risk predictors.[9,59] Although these studies suggest that the genetic risk score is a predictor of increased risk in middle-aged to older populations, they do not provide evidence for implementing the genetic risk score in practice. An additional challenge in implementing current genetic risk algorithms is that they are focused only on common genetic variants and do not take into account other potential contributors, including lower-frequency genetic variants, gene-by-environment interactions, levels of gene expression, and epigenetic background. For genetic risk scores to be of clinical utility, not only will it be necessary to show clear contribution to risk discrimination, but it is essential for the information to be actionable; that is, evidence will be needed to determine how health care or lifestyle should be modulated to manage risk as assessed from the knowledge of genetic factors. Finally, whether genetic risk scores will ultimately be more useful in younger populations in which baseline CVD risk factor burden is lower remains to be determined.

Pharmacogenomics

Warfarin is a widely used oral anticoagulant that has a narrow therapeutic index and wide interpatient variability, which makes dosing difficult and adverse drug events common (Table 2). *CYP2C9* and *VKORC1*, which encode the major drug-metabolizing enzyme and protein target of warfarin, respectively, have common polymorphisms that have been shown in numerous studies to affect warfarin dose requirements. These polymorphisms collectively explain up to 35% of warfarin dose variability.[45] Dosing algorithms have been developed that incorporate clinical, demographic, and genetic factors to estimate stable warfarin dose in

individual patients.[60,61] The dosing algorithms incorporating clinical, demographic, and genetic factors have been shown to be superior to clinical algorithms, the genetic dosing table in the warfarin product label, and standard 5-mg initial dosing.[61,62]

Three recently completed randomized, controlled, clinical trials provide further insights into the use of pharmacogenetics to guide warfarin dosing. The Clarification of Optimal Anticoagulation Through Genetics (COAG) trial was designed as an efficacy trial in which genotype and warfarin dose in the first month was blinded, the comparator arm was dosing warfarin with a clinical algorithm (which incorporated everything in the pharmacogenetic algorithm except genetics), and there was frequent international normalized ratio (INR) testing (7 INRs in first month). Overall, there was no significant improvement in the primary end point, time in therapeutic range (TITR), in the first month.[46] Blacks had significantly worse TITR in the pharmacogenetic arm, although it is important to note that well-described African ancestry alleles that are associated with warfarin dose were not included in the dosing algorithm. The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) published 2 separate trials. The first was similar to COAG in that it tested a genotype-guided strategy (CYP2C9 and VKORC1) against clinical factors alone and compared TITR at 12 weeks. The results demonstrated no difference (61.6% versus 60.2%); however, the genotype-guided group had slightly higher TITR at 4 weeks (52.8% versus 47.5%), although this was not the primary end point.[47] In a separate EU-PACT trial that could be described as an effectiveness trial, the participants in the comparator arm received a standard dose (eg, 10 mg on day 1, 5 mg daily on days 2 and 3), and INR testing after day 5 was at the discretion of the treating clinician in both arms.[48] EU-PACT found that genotype-guided dosing led to a significantly greater TITR compared with the control arm (67.4% versus 60.3%; $P<0.001$), fewer INRs >4, and quicker time to reach therapeutic INR. An accompanying editorial[63] emphasized that these trials focused on only the early initiation of anticoagulation therapy, not the important long-term outcomes, including bleeding and thrombosis, but overall underscored the limited utility of a pharmacogenomic-guided approach to warfarin initiation.

Clopidogrel is an antiplatelet agent important in the treatment of patients with acute coronary syndromes or those undergoing percutaneous coronary intervention in whom definite clinical benefit has been established[64] and consensus guidelines clearly recommend its use,[65,66] Clopidogrel is a pro-drug that must be converted to the active metabolite[67] primarily by *CYP2C19*. Functional genetics variants in *CYP2C19* lead to important variation in clopidogrel pharmacokinetics and resulting differences in the level of platelet inhibition achieved.[68,69] Most important and congruent with the pharmacokinetic data, *CYP2C19* functional variants have also been associated with differences in clinical outcomes in patients with acute coronary syndrome treated with clopidogrel, particularly those undergoing percutaneous coronary intervention.[70–73] Although these associations have garnered some controversy,[74] the line of evidence was compelling enough for the US Food and Drug Administration (FDA) to add pharmacogenetic information to clopidogrel labeling in 2010, and many experts consider the data consistent enough to possibly justify genetically guided clopidogrel therapy.[75]

Despite this regulatory decision, genetic testing to guide clopidogrel therapy has not become widespread. There is residual uncertainty about the effects on cost and outcomes if pharmacogenetic testing were put into place. Clinical trials or formal experiences to define this are limited to date,[76,77] and adequately sized trials of a pharmacogenetic strategy are needed to determine both the effectiveness and cost-effectiveness of a genetically guided dosing or treatment selection strategy. We are just beginning to see evidence in this regard, with 2 studies reported in late 2013. Xie and colleagues[78] published a small study in 600 patients receiving percutaneous coronary intervention from China who were randomized to genotype-guided treatment versus conventional therapy. The composite end point of major adverse coronary events at 180 days was 2.6% in the CYP2C19 genotype–guided arm and 9.03% in the conventional arm (P=0.001), with lower rates of death, MI, and stent thrombosis but not stroke. This study is the earliest to provide suggestion for outcomes benefits based on CYP2C19 genotype guidance of clopidogrel therapy, but it is unclear at present how these studies will affect the clinical uptake of *CYP2C19* genetic testing for clopidogrel. Newer agents in this class (ie, prasugrel and ticagrelor) are more potent and do not appear to have similar variability in platelet inhibition.[79,80] They are much more expensive, however, so if one could distinguish who needed the more potent agent and in whom clopidogrel would be satisfactory, substantial cost savings could be achieved. Unfortunately, only ≈5% to 12% of the overall variability in platelet response to clopidogrel can be explained by readily available clinical and laboratory characteristics, and only ≈5% to 12% of that overall variability is attributable to CYP2C19 genotype.[69,81] Although literature on the impact of genotype-guided approaches on clinical outcomes is beginning to emerge, it is important to remember that the very-high-risk genotypes (eg, CYP2C19 *2*2 and CYP2C9 *3*3) occur infrequently enough that it might be difficult in trials to show the benefit of a genotype-guided approach, yet that does not eliminate the potential individual benefit in those who carry these risk genotypes. How to strike the balance between population and individual benefit remains a challenge in genetics and pharmacogenetics.

Finally, although genetic tests for CYP variation are commercially available and often reimbursable, most cardiologists have not ordered nor acted on such testing and thus may be uncomfortable initiating this testing independently in the absence of additional education or systematic decision-support tools. Thus, although genetic testing appears reasonable to determine whether clopidogrel is an adequate option for some patients, more data are needed to conclusively demonstrate cost and clinical outcomes of a testing regimen, as well as educational efforts and institution-level implementation programs. When such data are available, logistics of testing will need to be improved and educational efforts and institution-level implementation programs will be needed to foster integration into clinical practice.

Novel Drug Targets in Development: PCSK9 Inhibitors

One of the more exciting areas of drug development that has emerged from recent genomics has been in cholesterol lowering. The new work focuses on the PCSK9 protein (Table 2). This protein was initially linked to elevated serum cholesterol in a study performed by French investigators looking for genetic explanations of hypercholesterolemia not caused by LDL receptor gene defects.[50] Subsequently, investigators at the University of Texas

Southwestern Medical Center identified relatively common nonsense variants in the gene encoding the same protein in patients with low levels of LDL cholesterol.[51] Subsequent cell biological investigations provided evidence that PCSK9 degrades the LDL receptor. Multiple pharmaceutical companies have now created PCSK9 antagonists that lower LDL levels.[49] PCSK9 antagonists can provide an additional ≈50% lowering of LDL cholesterol to maximal-dose statin therapy.[52] PCSK9 antagonists also work as monotherapies and thus can be used in patients who are statin intolerant.[53,54] The current PCSK9 therapies that are most advanced in clinical trials are injectable proteins that may need to be given every other week or monthly, which could help with the drug adherence problems that beset many oral preventive medicines. Whether PCSK9 therapies reduce the risk of CVD along with LDL levels remains unknown at this time.

Screening/Clinical Actionability

Pioneering work in the long-QT syndrome[82] and in hypertrophic cardiomyopathy[83] defined causal genes for these syndromes and uncovered novel biology that has had far-reaching implications.[84] In the last decade, the perceived utility of genetic diagnosis has paralleled the availability of increasingly efficient genotyping technologies. The initial spike in enthusiasm has leveled off as scientists, cardiologists, geneticists, and panels work through the best approaches to deliver these programs in formats that improve patient care and protect patients.[85]

This balance is already being disrupted by several emerging trends. Comprehensive whole-genome sequencing offers the potential to define genetic modifiers of the final phenotype. Attention to racial differences in genome sequences in patients will be important because findings have provided evidence that specific polymorphisms, including vitamin D–binding protein gene polymorphisms, are significantly different between blacks and whites.[86] Similarly, as the potential for genotype-driven therapeutics emerges, more rigorous approaches to determine whether a specific genetic variant is pathogenic or an innocent bystander are needed.[87] Analysis of whole-genome sequencing brings up the scenario of identifying variants of unknown significance. A genetic evaluation process in the clinic must be prepared to address variants of unknown significance.[88] Patient counseling both during the pretest informed consent and after the genetic testing is important to manage expectations and to help put variants of unknown significance into context for the patient.[88] The translational genomics community will have to begin to establish innovative ways to assess the relationship between genotype and phenotype. A focus on novel phenotypes, molecular pathways, and molecular disease modules and networks, rather than on single genes, will likely be necessary to exploit genetics for diagnostic use or therapeutic discovery.[89,90]

Steps to Move From Genetic Discovery to Translation: Future Directions

Figure 2 provides an overview of the process involved in translating a genetic discovery, including the time duration and estimated costs.[91] Table 3 provides an overview of future directions for translation, discussed in more detail below.

Funding Programs to Incentivize and Promote Translation

To ensure translational efforts and their ultimate clinical application, the National Institutes of Health (NIH) has established and continues to develop programs. The Clinical and Translational Science Award program, the first of these efforts, sought to establish facilitated, integrated mechanisms for early clinical proof-of-concept testing that would accelerate discovery relevant to human disease. Although the Clinical and Translational Science Award program is still relatively young in its evolution, the success of the program remains to be seen. It is encouraging to recognize that federal funding has been applied to this important initiative with ongoing plans for its continuance.

More recently, the Centers for Accelerated Innovations program was developed to accelerate translation through discovery. This program is designed to support the development of essential infrastructure, enabling technologies, and relevant educational and advisory programs at centers to help bridge discovery and commercialization of translatable technologies. This initiative requires coinvestment by the awardee institutions, partnering institutions, industry, and investment community and does so with the goal of selecting technologies with the greatest likelihood of developmental success. The Centers for Accelerated Innovations initiative requires processes for facilitating go-no-go decisions at different stages of the development process to minimize late-stage failure and to optimize developmental efficacy.

A central feature of these programs is the need to provide an environment in which translation, development, and commercialization are appreciated and valued. Doing so requires re-educating the typical academic community while working closely with industry and the investment community to facilitate this educational process. Removing barriers to more effective and productive partnerships between industry and academia will likely require reconsideration of how intellectual property is assigned, improvements in the rapidity with which contracts can be successfully negotiated, and reassessment of the role of local and national institutional review boards in reviewing study protocols, particularly those involving multicenter trials. The academic community will also need to carefully consider the structure and content of training programs in translational research that can prepare young investigators for careers in either academia or industry.

The NIH has also recently established the National Center for Advancing Translational Sciences (NCATS). The goals of NCATS include overseeing the Clinical and Translational Science Award program, providing required resources for the development of new therapies, promoting regulatory science, and providing molecular libraries for therapeutic screens. Establishing this umbrella organization within the NIH, as well as support for other complementary resources essential for translation (eg, the Electronic Medical Record and Genomics [eMERGE] network, a consortium of biorepositories linked to electronic medical records data for conducting genomic studies), sends a strong message to the community that the federal government is responding to the need for facilitating translation effectively.

American Heart Association's Science & Technology Accelerator Program

The American Heart Association launched the Science & Technology Accelerator program to speed up the processes for delivering lifesaving drugs, devices, and other innovations to patients and their families. The goal of the Science & Technology Accelerator program is to identify the most revolutionary, transformational innovations and to accelerate their journey from bench to bedside.

The Science & Technology Accelerator has assembled a multidisciplinary team of experts in CVD, stroke, medical device and drug development, regulatory affairs strategy, technology transfer, venture capital, investment strategy, and the law, including intellectual property law, to review proposed research ideas. The Science & Technology Accelerator is supported exclusively by earmarked donations and receives no funds from the American Heart Association general operating budget. The program funds clinical research through loans and investments, intended to return the original investment. The revenue generated provides repayment of the original investment. Additional revenue generated is invested back into the research accelerator program.

The first Science & Technology Accelerator investment is in CytoVas, an in vitro diagnostics company. The Vascular Health Panel of CytoVas has been shown to identify high-risk individuals among those who have normal lipid values and no other cardiovascular risk factors or among those at intermediate disease risk. The Vascular Health Panel has been shown to identify asymptomatic patients with diabetes mellitus who are at high risk for cardiovascular events.[99] What remains to be completed are the steps to link these observations of the associations with vascular risk to specific actions that can be taken on the basis of the Vascular Health Panel to mitigate that risk. At that point, successful translation from the bench to utility in clinical practice will have occurred.

Improved Phenotyping to Enhance Translational Possibilities

Improved phenotyping will be particularly critical in the setting of large observational or naturalistic data sets such as those based on electronic medical records and claims data, which are expected to be increasingly used in the future. For example, medication exposure is relevant to pharmacogenomic interactions, but substantial misclassification likely occurs with concomitant loss of power when drug exposure is classified dichotomously at a single time point. Modern medical informatics can provide time-updated and quantified drug exposure metrics via pharmacy claims for more granular data,[100] which should improve the power to detect differences in the association of drug exposure with outcomes and genetic factors, as well as infrequent adverse events ascertained only after drug approval and widespread adoption (pharmacovigilance). Taking full advantage of the great quantity of electronic medical record data across the spectrum of CVD will require improvements in this type of phenotypic characterization across all domains of data.[101] Some have called for the establishment of an electronic "phenome," allowing additional associations to be tested and discovered.[102] Clinical phenotyping can be shaped by existing data sets, including the NIH-sponsored database of genotypes and phenotypes (dbGaP), phenome-wide association studies,[103] the NIH-sponsored eMERGE, and existing clinical trial data sets repurposed with drug trials used as clinical systems perturbations.[104] We must realize, however, that despite

how vast these data sets are, they are limited by the bias implicit in conventional disease phenotyping (eg, inclusivity, parsimony, end-stage phenotype based) and by the limitations of detailed, quantitative (intermediate) phenotyping information essential for precise disease characterization and personalized medicine.

At the molecular and cellular levels, the NIH supports a library of integrated network-based cellular signatures (LINCS), there are broad efforts at developing a comprehensive molecular interactome, and one can functionally phenotype patient-derived cells (including iPSCs and their derivatives).[105] These physiological and clinical phenotypes can be combined with measurable cellular, biochemical, or molecular phenotypes amenable to routine analysis to develop a comprehensive assessment of global (patho) phenotype and ultimately its response to a therapeutic intervention.

Cardiovascular biomarkers have provided important new dimensions in terms of understanding pathophysiological processes and disease subgroups[106] but also have the potential to advance genomic discovery. Although unbiased genomic approaches alone have been successful,[2] there are limitations when applied to diseases of often vastly heterogeneous (sub) phenotypes (eg, hypertension, heart failure).[107] Layering on relevant biomarker modeling (eg, B-type natriuretic peptide levels) can generate important new discoveries[2] that not only improve our understanding of the disease process itself but may even suggest specific novel therapies. Opportunities for this type of approach abound, with a constant stream of new biomarkers and emerging technologies such as metabolomic profiling.[108,109] Combination approaches can then also be taken. Imaging data sets and orthogonal, unbiased physiological information offer additional elements that contribute to the detailed phenotyping process.

Systems Genetics and Network Medicine

Once individual genetic discoveries have been made, the field of systems genetics allows us to understand the architecture of complex genetic traits, including common complex diseases and disease traits such as atherosclerosis and heart failure. Systems genetics is a form of genetics in which one examines the effects of genetic variation not only on the complex traits of interest but also on intermediate molecular phenotypes such as transcript or protein or metabolite levels. The goal is to create a genotype-to-phenotype map across multiple biological scales in the context of the naturally occurring variations that contribute to the trait.[110–114]

A major application of systems genetics in the area of CVD will be to follow up GWASs. Such studies have identified dozens of loci contributing to CVD traits, including atherosclerosis, blood pressure, lipoprotein levels, obesity, diabetes mellitus, and heart failure.[92,93] However, this information will have relatively little impact until the loci are translated into the gene networks and pathways that drive the (patho)phenotype. Subsequently, it will be important to know how the alleles interact with each other and with environmental factors. This can be done on a gene-by-gene basis, as was elegantly done for a locus contributing to lipid levels and atherosclerosis.[115] Systems genetics provides an alternative, or complementary, approach for this goal, using global analyses of biological molecules in populations that vary for the clinical traits. Recent technological advances have

made it possible to quantitatively survey hundreds or thousands of biological molecules, from DNA sequence variation to epigenetic marks to levels of transcripts, proteins, and metabolites. For example, metabolite levels can be surveyed by mass spectrometry in the plasma of individuals in a population varying for a CVD trait. The relationship of the metabolite levels to the disease can then be investigated through genetic mapping, correlation, and mathematical modeling. If the levels of a metabolite map to one of the GWAS loci, it suggests the possibility that the metabolite of interest is involved in the pathway leading from genetic variation to disease. Similarly, if a metabolite correlates with the disease trait, it raises the possibility of a causal relationship. The same logic applies to other intermediate phenotypes such as transcript levels and protein levels, although these are more difficult to examine in human populations because of the inaccessibility of relevant tissues.[116–118]

Systems genetics data can also be used to model biological networks and to test for enrichment of known biological pathways in intermediate phenotypes differing between cases and controls.[114,119,120] To date, the pathways used to filter the genetic data are derived largely from the conventional (reductionist) experimental curated literature, which freely admits to a distinct bias. Future success in the identification of disease determinants will require the application of the holistic, unbiased molecular interactome, representing all potential (ascertainable) molecular interactions in a cell, organ, or tissue, as an essential filter through which to derive disease modules from genetic variants. This process, which serves as the conceptual basis for the new field of network medicine, has been applied to pulmonary arterial hypertension recently by Parikh and colleagues,[121] who were able to identify novel associations comprising a novel molecular pathway that is essential for the pathophenotype. In our opinion, simple genetic associations (GWAS based), covariance analyses, and contemporary system genetics will yield to these more integrative network approaches as an effective strategy for linking genotype to phenotype, accounting readily (functionally and statistically) for the true functional consequences of variants with small effect sizes in the process.

Scientific Tools to Facilitate Cell-Based Models

After genetic discoveries have been made and systems genetics have been used to place novel findings in their relevant biological context, several techniques are necessary to begin to understand the mechanism of the association between the gene or specific altered variant and disease. This section outlines the various tools that can be used to understand gene function in this context; these tools are highlighted in Table 4.

Induced Pluripotent Stem Cells

iPSCs from somatic cells were a major discovery in that they enable pluripotent adult stem cells to be isolated from adult somatic cells and, with the introduction of “reprogramming factors,” differentiate into multiple lineages.[122] iPSC studies are potentially limited by heterogeneity in the genetic backgrounds of the individuals recruited for iPSC generation, along with a variety of other potential confounders (differences between patients and control individuals with respect to sex, ethnicity, epigenetic status, methodology used to generate the iPSCs, in vitro artifact, etc). An alternative strategy is to start with a single pluripotent stem

cell line, whether a wild-type cell line or an iPSC line obtained from a patient with a particular disease variant, and to alter the cell line genetically: either introduce the variant into the wild-type cell line or "cure" the variant in the patient-derived iPSC line. In this study design, with the use of isogenic cell lines that differ only with respect to the disease variant, virtually all of the potential confounders mentioned above would be eliminated. Techniques used for genome editing are listed in Table 4.

Several recent studies have highlighted the ability to use genome editing to create human cellular models of disease.[125,135,136] Such human cellular models can be generated de novo in as little as 1 month, offering a significant time advantage over traditional animal models of disease and potentially lending themselves to high-throughput interrogation of DNA variants.

Genome-Edited Somatic Cells

The same genome-editing technologies that are being used in human iPSCs can be applied in cultured somatic cell lines. Although traditional cultured cell lines carry a number of disadvantages, the use of these cell lines can serve a purpose in acting as an initial rapid test of the hypothesis using genome editing.

Somatic Manipulation of Genes in Rodents

Rodent models of disease, whether mice or rats, remain the mainstay of biological investigation of gene function. Although rodent models are costly and time-consuming and have the potential disadvantage of having physiology that differs significantly from that of humans, new advances in technology have made it possible to use rodents as a robust and reasonably fast system with which to functionally interrogate novel disease-associated genes.

Knockout Mice

Genetically modified mice have represented the gold standard of disease models since the 1990s. Traditionally, they have been generated by homologous recombination in mouse embryonic stem cells, insertion of those cells into mouse blastocysts to generate chimeric mice, and breeding of the chimeric mice to yield heterozygous and then homozygous knockout mice. A similar approach is used to make "knock-in" mice in which specific alterations are inserted into the mouse genome. The primary disadvantage of knockout mice is that they routinely take more than a year and $100 000 to generate de novo. Accordingly, the International Knockout Mouse Consortium (http://www.knockoutmouse.org/), comprising several organizations in Europe and North America, has been working to create a complete library of gene knockouts in mouse embryonic stem cells that would be available to the scientific community.[127] This consortium has established many types of target modification, including time- and tissue-specific directed deletion of genes.

Knockout Rats

Unlike mice, rats have not seen widespread use as models of genetic diseases because rat embryonic stem cells were only recently isolated and successfully used to generate a genetically altered rat.[137] However, the genome-editing technologies that have made feasible

the manipulation of human cells are now being used to create knockout rats. The genetically modified rat strains are being made available to the scientific community through the Knock Out Rat Consortium.

Other Animal Models

Although rodent and larger animal models have played a central role in defining our understanding of the biology of the cardiovascular system, the sheer scale of genomic technologies is rapidly overwhelming our ability to model all of the novel insights that we have gleaned.[138] For example, community efforts to generate null alleles in every gene in the mouse have not been completed as a result of limited resources.[139] In addition, it has become apparent that even if embryonic stem cell lines can be generated for each gene, the ability of individual laboratories with phenotypic expertise to characterize at the genomic scale is rate limiting.[140] More tractable species will be required to prioritize experiments for empirical testing in more representative models. Among the relevant species are *Caenorhabditis elegans*, Drosophila, and zebrafish.[25,141]

Many genomic features can readily be modeled in *C elegans*, and efficient gene transfer and RNAi technologies enable genome-wide analyses on a time scale that approaches that of cell culture.[129] This is all feasible in an organism in which the origin of each and every cell has been specifically mapped.[130] The nematode (*C elegans)* has been a powerful tool for the exploration of molecular pathways and will continue to be as the tools for genetic manipulation expand.[129] The fruit fly has many of the advantages of the worm but a more advanced circulatory system with a segmented dorsal vessel that represents the heart and the aorta.[131] Despite an open circulation, there is high conservation of the genetic regulatory circuits between fly and humans.

Every organism offers a balance between representative physiology and pharmacology and tractability.[132] Transgenesis is highly efficient; gene knockdown is trivial; and genome-wide null allelic series are under construction. Gene editing is increasingly feasible, and reports of homologous recombination, however inefficient, raise the possibility of truly comprehensive modeling at scale.[133] Screening is feasible in the 96-well plate format in an automated or a semiautomated configuration.[134] At present, phenotyping technologies are the rate-limiting step.

Moving to Clinical Application: How Gene Targets Can Ultimately Be Translated Into Therapeutics

This section details how gene targets move through the process to drug development. The current steps are outlined, as well as insights into methods of identifying drug targets that might ultimately be more efficacious than traditional methods. An overview can be found in Table 3.

Rational Polypharmacy and Drug Target Selection

The decreasing productivity of the pharmaceutical industry, despite an increasingly refined approach to identify and structurally characterize potential drug targets, can be interpreted to

suggest that the drug discovery process is inadequate. Drugs do not operate in a vacuum and alter 1 identified target in isolation. Targets exist within networks of interconnected molecules. Small-molecule therapeutics are likely to interact with more than single targets, a property that likely accounts for unexpected (off-target) effects. Analyzing the consequences of drug exposure in a global phenotype(s) seems a more prudent course of drug development than analyzing target-based screening. Recent data show that this is correct. Phenotype screening is more successful than target-based screening in achieving FDA-approved therapeutic entities, even in this current era of exquisitely detailed drug target structural and functional information.[94]

The underlying basis for the success of phenotype screening is that it provides the integrative effect of a drug on the entire system (cell, organ, organism) in which it operates. This system is a network of interacting molecules, some of which serve as drug targets. Understanding the consequences of a drug on the system requires an integrated approach that first recognizes or constructs the topology of the network and then analyzes the dynamics of the network; either property of the network can be affected by the perturbation of the drug. This paradigm defines the field of systems pharmacology, which offers a new approach for drug development. For this approach to be most effective, the phenotypes of the preclinical models need to reflect human disease accurately. An excellent overview of the current limitations of the preclinical models in CVD is provided elsewhere.[142]

In addition to understanding the effect of a drug on a meaningful phenotype and ascertaining the effect of a drug on a potential unwanted action, systems pharmacology provides the basis for “rational polypharmacy,” or the development of drugs used in combination to affect a pathway or a phenotype. Rational polypharmacy offers the opportunity to minimize the development of drug resistance (in antimicrobials or antineoplastic therapies), to minimize side effects of any single agent by optimizing synergies, and to rewire a network of molecules that drive a pathophenotype, restoring its function homeostatically toward healthy activity.

Preclinical Toxicology

To test a new drug in humans in either healthy volunteers or patients with the medical condition that is targeted for treatment, the FDA requires that the drug must first undergo toxicological testing in animals. Typically, testing must be done in 2 different species, commonly a rodent and a nonrodent, and the duration of the toxicology study must encompass at a minimum the length of time that the initial human study will be conducted. The goal is to identify a dose that produces no observable adverse event in the animals so that a significantly lower dose can be used as the starting point for testing in humans. These dose calculations are adjusted for body weight and potential metabolic differences between species to yield a human-equivalent dose, and then a decrease of 10-fold typically is used to provide an additional safety margin for the human trial. Another goal of the toxicology work is to identify the target organs of toxicity so that safety monitoring can be engineered into the clinical development plan. The cost of toxicology studies ranges from $250 000 up to $1.5 million, depending on the number of doses tested, the duration of the treatment, and the choice of species. The species choice is affected by many variables. Small-molecule

therapeutics typically have a broad choice, whereas protein therapeutics such as antibodies must find a primate species with a target protein that is also bound by the therapeutic protein. In some cases, these necessitate the creation of a toxicology test protein that specifically recognizes the animal drug target but will not be the therapeutic molecule that is tested in humans. Regardless of what is required, finding the financial resources needed to conduct the toxicology studies required by the FDA is frequently a major barrier to drug development in the academic arena. Recognizing this limitation, the NIH has established a number of programs to overcome this obstacle.

Replacing an older program called Rapid Access to Intervention Development, the Bridging Interventional Development Gaps program was launched in October 2011. The program is run under the auspices of NCATS, and investigators are provided access to NIH subcontractors who are qualified to conduct Investigational New Drug, enabling pre-clinical studies. (The process for investigators is competitive.) The NIH pays for these services on behalf of the investigator. In addition to toxicology services, these contractors can support the synthesis and formulation of new drugs and pharmacokinetic studies in appropriate animal species. Contract costs are supported by the NIH Common Fund and by collaborating NIH institutes and centers. More details about the Bridging Interventional Development Gaps program can be found at the NCATS Web site (http://www.ncats.nih.gov/research/rare-diseases/bridgs/bridgs.html). Individual NIH institutes may also have programs similar to Bridging Interventional Development Gaps. For National Heart, Lung, and Blood Institute–funded investigators, a program called The Science Moving Towards Research Translation and Therapy is providing access and funding to facilities that can assist investigators with small-molecule and biologics synthesis, pharmacology, toxicology, and clinical trial coordination (www.nhlbi.nih.gov/news/spotlight/fact-sheet/smartt-speeding-the-translation-of-discoveries-to-the-clinic.html).

Rescuing and Repurposing Drugs

The NIH has created an initiative to make available drugs previously generated by the biopharmaceutical industry that academic investigators can now use to test their utility against new targets or in new disease indications. Sponsored by NCATS, the pilot program is titled Discovering New Therapeutic Uses for Existing Molecules (http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html).

Some of the world’s largest pharmaceutical firms have collectively provided dozens of molecules that have already been tested in humans for ≥1 indications. Because these compounds have previously entered the clinic, they should be deployable in novel human clinical trials with very little additional preclinical work needed to secure FDA approval for those new studies. Because a substantial investment in toxicology, pharmacokinetics, and pharmacology has already been made in these compounds, investigators who successfully apply for grant funding for the use of these compounds are able to leverage this multimillion dollar investment in a new disease area. The pilot program was initiated in fiscal year 2013 with funding of $20 million to support the new studies, provided in the form of 2- to 3-year grants using a staged, cooperative agreement structure. The program has some important restrictions such as requiring that proposals must use the drugs in their current formulation

state (eg, if the drug was created as an oral medicine, an application calling for reformulation to enable intravenous delivery would be considered a nonresponsive proposal). Repurposing has many attractions, but investigators should also be aware of some potential limitations of the use of drugs that have never attained marketing approval by the FDA. These drugs will still require substantial development in phase 2 and 3 studies to secure approval for broad use. A list of the currently available compounds, their molecular targets, and the indications for which they were originally developed is provided by NCATS (http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/directory.html).

Clinical Trials and Postmarketing Research

Once drug targets are identified and medicines are developed, they are classically approved by the FDA through a process involving clinical studies that consist of 4 phases (Table 5 provides a description of the 4 phases). For some disease conditions such as diabetes mellitus, the FDA has recently issued guidelines that require that drugs that lower blood glucose must also establish that they have no cardiovascular safety signals before attaining approval. This can be accomplished in multiple ways, but one route is for the sponsor to show that there is no large adverse impact on cardiovascular health in the initial approval package and then commit to performing a substantial postapproval study that confirms the cardiovascular safety of the drug. These studies require a cardiovascular team that can adjudicate morbidity and mortality events in large-scale, multicenter clinical trials.

These studies can focus on new uses for a drug that may have little commercial appeal to the original drug manufacturer but fulfill an important unmet medical need. The use of an approved drug for a new indication is often best accomplished by filing a new Investigational New Drug with the FDA. Typically, the investigator is able to cite all the regulatory filings of the original manufacturer in this Investigational New Drug filing; however, this requires cooperation from the original manufacturer. An investigator who identifies a new use for an already approved drug may file a method-of-use patent that claims this new utility. This patent would preclude the original manufacturer from marketing the drug for the new utility without first obtaining a license from the academic investigator's institution. The academic investigator does not have patent rights on the drug itself and cannot sell the drug for the new use without violating the original manufacturer's patent until that patent expires. Leveraging a working relationship between academics and drug manufacturers enables the broadest possible use of drugs for which new indications have been discovered.

Systems Pharmacology and Clinical Trial Design

New techniques may help speed up the process of drug target design and testing. The principles of systems pharmacology can be applied across the continuum of drug discovery, drug development, and drug use, including next-generation clinical trial design.[96–98] To test increasingly personalized therapies derived from robust analysis of the system within which a drug or drugs are believed to operate, unique trial design strategies will be necessary.[143] Because of rapid advances in the ascertainment of the systems responses and their genomic, proteomic, or metabolic determinants,[144,145] as well as the need to optimize drug dosing

with the use of a rational polypharmaceutical strategy, clinical trials must undergo targeted modification during their course. These changes in trial design imply that the key elements of the trial (population size, dosing, combinations of agents, timing of agent administration) will be modified, often post hoc in response to the acquisition of new knowledge. Adaptations to clinical trial design can occur for 1 of 3 reasons: new information from a source external to the trial, a prospectively planned interim analysis of the trial data, and unplanned findings that arise from an interim analysis. The first 2 reasons are referred to as reactive revisions; the third is referred to as an adaptive design. Adaptive designs have been used in clinical oncology for many years and have met with some success. The parameters used to devise these trial adaptations progressively limit the sample size in each treatment cell; however, with continued refinement of the trial design informed by new information, there is also likely to be an increase in the expected effect size. This latter improvement would be expected to offset the loss of, if not enhance, the statistical power of the evolving study. The trial design principles governing adaptive changes are becoming increasingly refined. Clinical trialists and the community of practitioners involved in systems-based, rational polypharmacy will need to work closely with regulatory authorities (in this country, the FDA)[145] to ensure that these in-trial changes in trial structure meet the standards needed to adequately assess the efficacy and safety of a therapeutic strategy.

Summary

Slow Progress and Unmet Expectations for Direct Clinical Application

A promise of the emerging discoveries in the area of genetics and genomics is that analysis of each person’s genome will lead to personalized genomic and preventive medicine. As we have detailed in this scientific statement, even the most strongly implicated DNA sequence variation with human disease often accounts for merely a small component of risk when examined in isolation (as is typically done in GWASs), limiting the use of genetic risk prediction as a meaningful clinical implication of this work. More important, however, the identification of novel genetic signals will elucidate new pathways and mechanisms of disease, thus providing novel drug targets.

We have outlined and provided insight into the various steps involved once a genetic discovery has been made to its ultimate clinical applicability, with most of our attention focused on therapeutics development. As evidenced in Figure 2, the duration of this process can take on average 15 to 20 years, with a cost of nearly $1.7 billion per successful new therapeutic.[91] It is our hope that in the next decade, the results of the emerging discoveries in the area of genetics and genomics will permit better drug design and genetically targeted therapies that will serve to speed up this process. Ultimately, the path from gene discovery to implementation in the clinic remains a multistep process that requires years of research and testing.

To make this process as efficient as possible, we need to accelerate translation and implementation. It is also critical that the public expectations and perception of the process of translation be based on realistic goals and timelines for the translational process to occur. In addition, the costs of moving new genetic discoveries along the translational pipeline are high, highlighting the importance of adequate funding at each level of development.

Conclusions

The field of genetics and genomics has exploded in the last few years, with thousands of newly discovered genetic loci in association with human health and disease. These loci have the potential to shed new light on the mechanisms and pathways of human disease and offer several new avenues for clinical discoveries. However, this process takes time, underscoring the need for a recalibration of the expectations of both the scientific and lay community as we await the realization of clinical utility from the explosion of new findings in the area of genetics and genomics.

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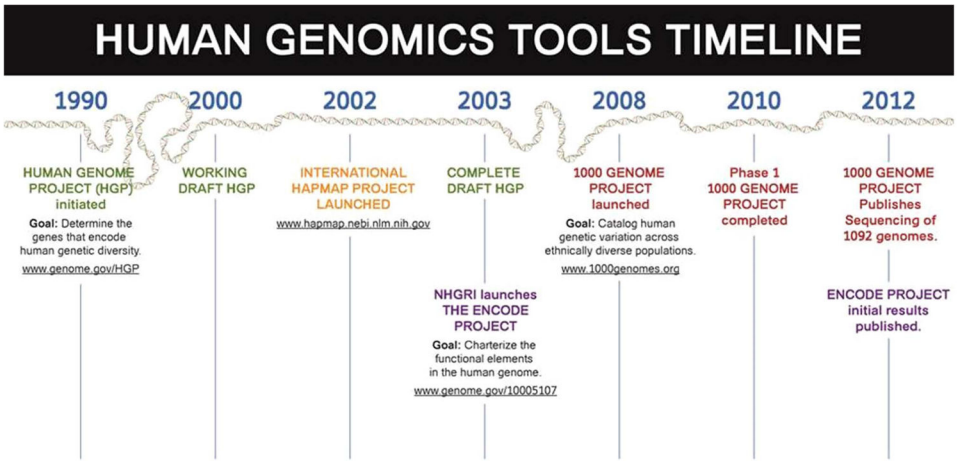

Figure 1.

Timeline of the emergence of key tools to enable rapid discovery in the area of genetics and genomics. ENCODE indicates Encyclopedia of DNA Elements; and NHGRI, National Human Genome Research Institute.

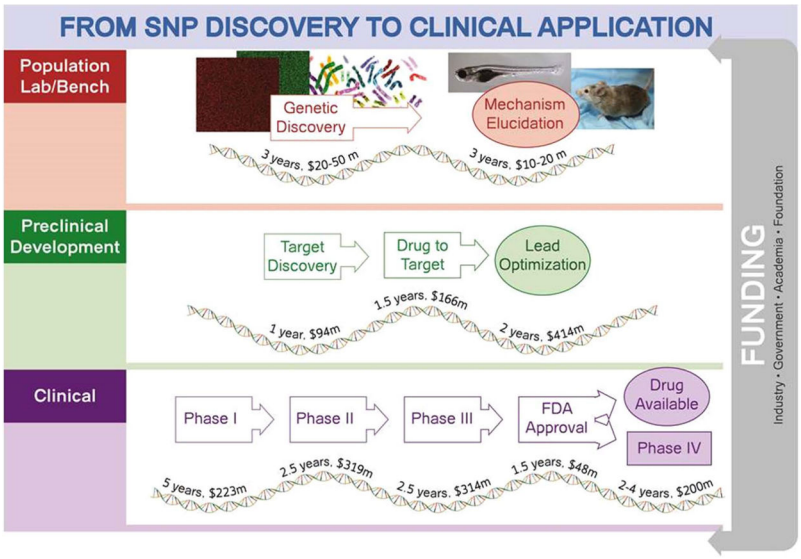

Figure 2.

Steps, timeline, and approximate costs for the key steps from single-nucleotide polymorphism (SNP) identification to achieving clinical utility. Timeline and costs based on Paul et al.[91] The figure should be read from left to right, starting at the top. Please note that the timeline reflects the current pace of drug development. We acknowledge the National Human Genome Research Institute Digital Media Database for the elements in this schematic (http://www.genome.gov/dmd/). FDA indicates US Food and Drug Administration.

Table 1

Examples of Genomic Discoveries That Have Translated Into Currently Used Clinical Therapies

Therapy	What Does It Do?	Studies
Statin	Reduces LDL cholesterol and CAD risk	Pioneering studies identified a defect in the LDL receptor, preventing the mutant LDL receptor from normally clearing LDL cholesterol from the blood.[21,22] Mechanistic work identified HMG CoA reductase, which led to the development of the first HMG CoA reductase inhibitor, or statin, in clinical practice in 1987, which substantially reduced the rate of coronary heart disease events.[23]
Imatinib	Tyrosine kinase inhibitor used to treat patients with chronic myeloid leukemia	Imatinib was the first tyrosine kinase inhibitor to receive approval from the FDA. Select patients fail or become intolerant to therapy, leading to second-generation therapeutics.
Ivacaftor	Small-molecule potentiator of CFTR. Ivacaftor was approved for the treatment of patients with cystic fibrosis who harbor a G551D mutation in the CFTR gene, which impairs the ability of CFTR at the cell surface to open.[24]	High-throughput membrane potential assays were designed to identify CFTR potentiators and led to the development of ivacaftor. This drug improves chloride transport by potentiating the open probability of the G551D-CFTR mutated channel.

CAD indicates coronary artery disease; CFTR, cystic fibrosis transmembrane conductance regulator; FDA, US Food and Drug Administration; and LDL, low-density lipoprotein.

Table 2

Emerging Clinical Tools From Recent Discoveries in the Area of Genetics and Genomics

Emerging Science	Role	Pioneering Studies
CVD risk prediction	Genetic risk prediction uses genetic information to predict who is at risk for an MI; it has not demonstrated improvement in risk discrimination.	A genetic risk score using SNPs associated with clinically apparent coronary heart disease or MI predicts the risk of future CVD events independently of other risk factors[44] but provides only small to modest evidence for reclassification and no improvement in discrimination for future CVD events.
Pharmacogenomics	Uses genetic information to guide dosing or medication selection, most prominently warfarin and clopidogrel	*CYP2C9* and *VKORC1*, which encode the major drug-metabolizing enzyme and protein target of warfarin, respectively, have common polymorphisms that have been shown in numerous studies to affect warfarin dose requirements, collectively explaining up to 35% of warfarin dose variability.[45] Despite this, large, randomized, controlled trials have been mostly disappointing,[46–48] and genetic-guided pharmacological warfarin and clopidogrel dosing has not found its way into clinical practice.
PCSK9 inhibitors	PCSK9 antagonists lower LDL levels by inhibiting LDL receptor degradation, allowing more LDL to be cleared from the blood.[49]	*PCSK9* was initially linked to elevated serum cholesterol in a study performed by French investigators looking for genetic explanations of hypercholesterolemia not attributable to LDL receptor gene defects.[50] Investigators at the University of Texas Southwestern Medical Center identified single-allele mutations in the gene encoding the same protein in patients with low levels of LDL cholesterol.[51] Subsequent cell biological investigations have provided evidence that PCSK9 works by regulating the degradation of the LDL receptor. PCSK9 antagonists can additionally lower LDL cholesterol by ≈50% in patients on maximal-dose statin therapy.[52] They also work as monotherapies and can be used in patients who are statin intolerant.[53,54]
Screening/clinical actionability	Identifying individuals at risk through the use of genetic testing	The emergence of next-generation sequencing as a clinical tool has made it apparent that the interpretation of genomic data will face several hurdles on the road to meaningful actionability.[17,55] The predictive utility of a single genetic variant is largely a function of the strength of the correlation with a specific phenotype, so genotype often adds little to the clinical situation because the clinician can rely on it only in the setting of high penetrance.

CVD indicates cardiovascular disease; LDL, low-density lipoprotein; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; and SNP, single-nucleotide polymorphism.

Table 3

Steps to Facilitate Genetic Discovery to Translation

Tools	Specific Programs/Tools	What It Does
Scientific programs	Clinical and Translational Science Award program	Integrated mechanisms for early clinical proof-of-concept testing to accelerate discovery relevant to human disease
	Centers for Accelerated Innovations	Supports the development of an essential infrastructure, enabling technologies, and relevant educational and advisory programs at centers to bridge the chasm between discovery and development in commercialization of translatable technologies
	NCATS	Oversees the CTSA program, making available critical resources required for the development of new therapies, promoting the notion of regulatory science to facilitate effective and efficient evaluation of novel diagnostics and therapeutics, and providing molecular libraries for therapeutic screens
	AHA Science & Technology Accelerator Program	AHA program designed to speed up the processes for delivering lifesaving drugs, devices, and other innovations to patients and their families
Phenotyping	Physiology and clinical detail of human health and disease	Enhanced phenotyping can improve power to detect meaningful associations and advance our ability to apply them clinically.
Systems genetics	Integration. The goal is to understand the architecture of complex genetic traits and to create a genotype-to-phenotype map.	Major application will be to follow up GWASs. Such studies have identified dozens of loci contributing to cardiovascular disease traits, including atherosclerosis, blood pressure, lipoprotein levels, obesity, diabetes mellitus, and heart failure[92,93] which will have little impact until the loci are translated into genes pathways, networks, and (unbiased, network-integrated) disease modules.
Rational polypharmacy and drug target selection	Analyzing the consequences of drug exposure for measurable, global phenotype(s) as a future course of drug development may be more successful than traditional target-based screening.	Phenotype screening is more successful than target-based screening in achieving FDA-approved therapeutic entities, even in this current era of exquisitely detailed drug target structural and functional information.[94]
Preclinical toxicology	FDA requirement that a novel medicine must first undergo toxicology tests in animals	Identifies a dose of a new medicine that produces no observable adverse event in the animal so that a lower dose can be used as a starting point for testing in humans
Efficacy testing	Tests the effectiveness of a therapeutic intervention	Will require developing a new disease taxonomy that would define diseases on the basis of their intrinsic pathobiology and their conventional clinical phenotype[95]
Rescuing and repurposing drugs	Initiative to make available drugs previously generated by the biopharmaceutical industry that academic investigators can now use to test their utility against new targets or in new disease indications	Sponsored by the NCATS, the pilot program is titled Discovering New Therapeutic Uses for Existing Molecules (http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html).
Postmarketing research	Studies of drug safety that occur after the medicine is available	For some disease conditions such as diabetes mellitus, the FDA has recently issued guidelines requiring that drugs that lower blood glucose must also establish that they have no cardiovascular safety signals before attaining approval.
Systems pharmacology	Network of interacting molecules, some of which serve as drug targets	Application of the principles of systems pharmacology across the continuum of drug discovery, drug development, and drug use, including in next-generation clinical trial design[96–98]

AHA indicates American Heart Association; CTSA, Clinical and Translational Science Award; FDA, US Food and Drug Administration; GWAS, genome-wide association study; and NCATS, National Center for Advancing Translational Sciences.

Table 4

Scientific Tools to Enable Translation of Findings From the Area of Genetics and Genomics

Scientific Tool	Description	What It Does
iPSCs	Induced pluripotent stem cells pioneered by Takahashi and colleagues[122]	Introduction of "reprogramming factors" into fibroblasts or other differentiated cell types
Genome-edited pluripotent stem cells	Genome-editing approaches include zinc finger nucleases,[123] transcription activator-like effector nucleases,[124] and CRISPR,[125,126] among others.	Genetically alter a cell line to remove confounders that may occur in the study of iPSCs
Genome-edited somatic cell lines	Genome editing is performed as above.	Application of genome-editing technology to cultured somatic cell lines
Somatic manipulation of genes in mice	Genetically modified mice have represented the gold standard of disease models since the 1990s. Methodology for somatic manipulation includes overexpression of target gene via adeno-associated gene delivery to mouse liver, knockdown of target genes via siRNA delivery, transcription activator-like effector nucleases, and zinc finger endonucleases.	New advances in technology have made it possible to use rodents as a robust and reasonably fast system with which to functionally interrogate novel disease-associated genes.
Knockout Mouse Consortium	International Knockout Mouse Consortium (http://www.knockoutmouse.org/)	Working to complete a library of gene knockouts in mouse embryonic stem cells[127]
Knockout Rat Consortium	Rats did not previously have widespread use of genetic models of disease until recently, when genome-editing technologies have made feasible the manipulation of human cells and now are being used to create knockout rats.	Genetically modified rat strains are being made available to the scientific community through the Knock Out Rat Consortium.[128]
Caenorhabditis elegans	Nematode that has served as a powerful tool to explore molecular pathways (http://www.wormbase.org)	Genomic features can be readily modeled; efficient gene transfer techniques exist.[129,130]
Fruit fly	Fruit fly has many advantages of *C elegans* and has a more advanced circulatory system and segmented dorsal vessel that represents the heart and aorta[131]	Model organization for mechanism elucidation that has high conservation with humans
Zebrafish	Fish model that offers a unique balance between physiology, pharmacology, and tractability	Highly efficient gene knockdown[132–134]

CRISPR indicates clustered regularly interspaced short palindromic repeats; and iPSC, induced pluripotent stem cell.

Table 5

Phases of Clinical Trials

Phase	What Is the Goal?
1	Test the safety and tolerability of a new medicine in healthy volunteers
2	Test efficacy in small numbers of patients with a medical condition of interest and identify a range of doses for subsequent testing
3	More substantial test of efficacy and safety in patients (called the pivotal or registration trials)
4	Follows FDA approval. Additional studies are conducted by the sponsor to further refine the disease population or to extend the use of the drug into populations not studied in the original New Drug Application or to define additional outcomes that increase the value of the drug.

FDA indicates US Food and Drug Administration.