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Building a Program in Translational Genomics

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Abstract The goals of this article are to define translational genomics and assess the need for programs in translational genomics. The benefits of developing a translational genomics program will be outlined from a clinical perspective, a research perspective, and a consumer perspective.

Keywords Genetic · Genomic · Heart · Translational · Congenital

Ischemic and cerebrovascular heart disease rank as the number one and number two leading causes of death in *developed* countries (WHO World Health Report 2002). In *developing* countries, ischemic and cerebrovascular disease rank as the third and fifth leading causes of death (WHO World Health Report 2002). A goal of programs in translational genomics is to understand how genes influence cardiovascular disease.

Cardiovascular disease is a broad net that includes many different types of disorders involving the heart and vasculature, as well as other cells and tissues in the body that are only recently being discovered. Genetics contribute to cardiovascular disease. The contribution of DNA to risk for cardiovascular disease varies with each individual and depends on the specific type of disorder. Cardiovascular disease is currently divided into "single-gene" disorders and "complex-genetic" disease. Single-gene disorders are thought to arise from structural variation in a single gene. This genetic variation may result in a clinical phenotype such as a decreased ejection fraction. The resulting phenotype(s) of a single-gene disorder may also be influenced by the underlying genetic map of the individual, interactions with the environment, behavior, social economic status, and chance. Complex disease is thought to arise from structural variations in several genes that lead to clinical phenotypes such as high blood pressure, coronary artery disease, or myocardial infarction. A major component of complex disease also includes genetic interactions with behavior, environment, social economic status, and chance. It is predicted that as we learn more about the structural variation in the human genome, these categories of single-gene disorders and complex-genetic disease will be re-defined.

Translational genomics may be defined as the study of genes in health and disease in the clinic and laboratory. The types of research conducted may include a blend of population genetics, clinical research, molecular and cellular biology, gene expression, chemical screening, and epidemiological research. A program in translational genomics bridges the clinic and the research. A strategy map shown in Fig. 1 shows the benefits of a program in translational genomics from a clinical perspective, a research perspective, and a consumer perspective. As seen in Fig. 1, the consumer benefits of a program in translational genomics include improved quality of care, improved quality of life, and convenience. Improved care stems from a staff that includes genetic counselors and clinician scientists that are trained in the role of genetics in

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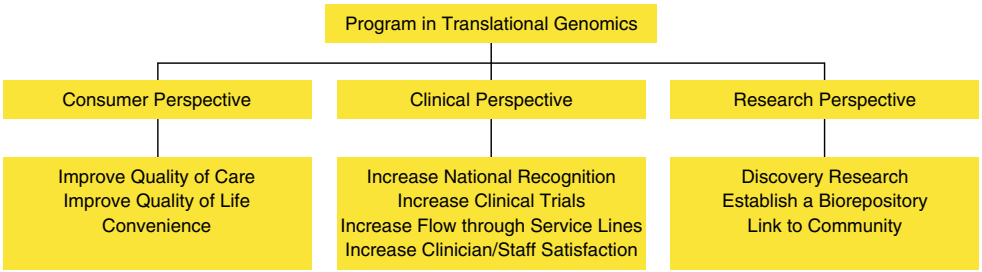

Fig. 1 A strategy map showing the benefits of a program in translational genomics from a clinical perspective, a research perspective, and a consumer perspective

cardiovascular disease. Convenience to the patient on a day to day basis is important. Clinicians, scientists, and staff have the ability to improve convenience to the patient by screening their family members and making time for the family during the visit.

From a clinical perspective, a program in translational genomics offers medical centers an opportunity for national recognition as a training center for young clinician scientists, and as a tool to increase awareness of clinical trials and service lines to the community. The clinical center gains recognition in nationally recognized journals. Involvement in a program in translational genomics often increases clinician and staff satisfaction - which in turn improves consumer care and decreases clinician and staff turnover.

From a research perspective, a translational genomics program provides a bridge between the clinic and the laboratory. The program directors may also provide the strategy for the leaders of the institution to align with the NIH mission to define the underlying etiology of diseases. In summary, a program in translational genomics benefits the patients, the clinics, and the research programs.

Table 1 separates CVD into three areas for the purpose of building a program in translational genomics: single-gene disorders, complex disorders, and congenital heart disease. Congenital heart defects arise from both single-gene disorders and complex disorders. Several examples are listed for each area. All three (single-gene disorders, complex disorders, and congenital heart disease) share clinical and research commonalities, yet have unique aspects that need to be recognized as one builds a program. The table is not meant to be comprehensive but rather provide a sampling of the differences between the three areas.

Single-gene Disease

Single-gene (Mendelian) disorders are currently thought to include familial cardiomyopathies; channelopathies, including long QT syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia; familial hypercholesterolemia; familial (primary) pulmonary hypertension; and Marfan syndrome [3, 4]. Genetic testing now exists for many of these genes [4]. Thus, an important arm of any translational genomics program is a genetic counselor working in the clinic to help identify patients at risk of a single-gene disorder. The genetic counselors may construct the pedigrees, draw the blood samples, coordinate the genetic testing, and educate and discuss the findings with the patient and the family members. This will have an immediate impact on the patient and also provide early detection for the family members (that may be screened or tested).

Complex Disease

In the case of complex diseases such as coronary heart disease, stroke, and hypertension, the contribution of genetics is still unclear. Genetic variation in several genes may contribute to the overall risk of disease. In addition,

Table 1 This table separates CVD into three areas for the purpose of building a program in translational genomics: single-gene disorders, complex disorders, and congenital heart disease

Single-gene disorders	Complex disorders	Congenital heart disease
Familial-dilated cardiomyopathy	Coronary artery disease	DiGeorge syndrome
Hypertrophic cardiomyopathy	Stroke	Williams–Beuren syndrome
Familial-restrictive cardiomyopathy	Hypertension	Alagille syndrome
Arrhythmogenic right ventricular dysplasia		Noonan syndrome
		Holt–Oram syndrome
		Nonsyndromic single-gene disorders [1]

All three share clinical and research commonalities yet have unique aspects that need to be recognized as one builds a program. The table is not meant to be comprehensive but rather provide a sampling of the differences between the three areas. A more complete listing of Congenital Heart Defects can be found in a white paper from the AHA Congenital Cardiac Defects Committee [2].

environmental factors, social economic status, behavior, and chance also play a role. A program in translational genomics serves unique roles in the case of complex diseases. Involving genetics in clinical research trials where genetic information is linked to phenotypic information will help move the field forward. Providing genetic information or services for the patient at this point is less clear. The role of a genetic counselor in the clinic with direct patient care and management is evolving. How much emphasis to place on recently identified genetic variants that increase risk of coronary artery disease or myocardial infarction [5–7] is challenging. An interval on chromosome (region 9p21) was recently identified by three independent studies to be associated with coronary heart disease and myocardial infarction [5–7]. It is estimated that 20–25% of Caucasians are homozygous for this risk allele. Homozygosity for the risk allele increases risk of coronary heart disease by 30–40%. Although testing a patient for this mutation may be seen as a positive, it certainly does not provide a full picture for the patient in terms of his/her full risk profile.

Congenital Disease

The last category to be discussed is congenital heart disease. This has been separated into its own category for the purpose of building a translational genomics program. A reason is that these patients and their families greatly benefit from genetic counselors. Identification of a genetic cause of disease is many times beneficial and allows confidence in the diagnosis and exact explanation of the underpinnings of the disease [2]. As discussed in a white paper put out by the AHA Congenital Cardiac Defects Committee, knowing the genetic cause of the disease also allows the clinician to investigate other organ systems that may be involved in the syndrome [2]. It permits for greater phenotyping of traits in other family members [2]. Mendelian and chromosomal syndromes are estimated to account for 20% of all congenital heart disease [8]. We do not know the underlying mechanisms accounting for the remaining 80% of congenital heart disease. However, as more information unfolds regarding the structural variation in the genome, it is likely that copy number variation and somatic mosaicism may both play a

Table 2 Components needed for establishing a program in translational genomics for single-gene disorders, complex disorders, and congenital heart disease

Single-gene disorders	Complex disorders	Congenital heart disease
Staff	**Staff**	**Staff**
Genetic Counselor	Genetic Counselor	Genetic Counselor
Clinical Nurse Coordinator	Clinical Nurse Coordinator	Clinical Nurse Coordinator
Biostatistician	Biostatistician	Biostatistician
Computer Scientist	Computer Scientist	Computer Scientist
Postdoctoral fellow	Postdoctoral fellows	Postdoctoral fellows
Research Technician	Research Technician	Research Technician
Scientist	Scientist	Scientist
Clinician	Clinician	Clinicians (pediatric, adult)
		Link to Surgery
		Link to Ob/Gyn
Molecular and Genetic Laboratory	**Molecular and Genetic Laboratory**	**Molecular and Genetic Laboratory**
(Limited repository or discovery research)	Storage for DNA, −20°C to −80°C	Storage for DNA, −20°C to −80°C
Storage for DNA, −20°C to −80°C (±)	Storage of cells/tissue—cryovials, −80°C	Storage of cells/tissue—cryovials, −80°C
Robot (±)	Robot	Robot
DNA isolation (±)	DNA isolation	DNA isolation
Sequencing capabilities (±)	Sequencing capabilities	Sequencing capabilities
	CNV Platforms	CNV Platforms
	Model Organisms	Model organisms
Biomedical Informatics Resources	**Biomedical Informatics Resources**	**Biomedical Informatics Resources**
Registry and Network	Registry	Registry
Database with multiple types of data to be shared	Database with multiple types of data to be shared	Database with multiple types of data to be shared.
Early detection Program (Family)	Access to genome-wide association data and analysis tools	Fine Mapping
Pathways Programs	Pathways Programs	Model organism data
Fine Mapping		Pathways Programs

role as underlying causes for congenital disease [2, 9]. (A copy number variant has been defined as a deletion or duplication of ~1 kb or greater change in copy number in a genome compared to a reference sequence. Somatic mosaicism is defined as the presence of genetically distinct populations of somatic cells in a single organism.) A clinical program in congenital heart disease that includes a team of genetic counselors working alongside the team of clinicians and surgeons and other professionals is helpful for emphasizing compassionate patient care. An active clinical trials research program is also important for education and advancing/testing models of care. A model that works well is one that includes direct communication and close proximity between pediatric cardiology, adult cardiology, ob/gyn, and surgery and genetic counseling.

Building Blocks Table 2 describes needed for establishing a program in translational genomics for single-gene disorders, complex disorders, and congenital heart disease. Many of the blocks are overlapping. A goal is to combine compassionate patient care with research. The goal is to understand how genes influence disease.

Staffing requirements for programs focused on single-gene disorders and congenital heart disease include accredited genetic counselors and clinical nurse coordinators. Staffing suggestions for programs in complex cardiovascular disease are similar—although the role for genetic counselors in complex disease are likely very different from those in programs focused on single-gene disorders and congenital heart disease. An excellent overview on genetic counselors is included in this issue by Bonnie LeRoy. Also, see box 1

Box 1
NBGC= National Board of Genetic Counselors www.nbgc.org

ABGC = American Board of Genetic Counseling www.abgc.org

for URL link to National Board of Genetic Counselors and American Board of Genetic Counseling. The staff of genetic counselors works hand in hand with the medical professionals in the clinic. The clinical staff also includes a group of clinical research coordinators to bridge the clinic to the laboratory.

The role of a genetic counselor in a complex cardiovascular disease clinic is less well defined and still evolving. However, this should not decrease the weight of importance on the position, and may enhance the need for a genetic counselor in this time of change and uncertainty. Examples of the questions a genetic counselor may face would be genotyping for risk loci that have been recently shown to increase risk of coronary artery disease (9p21), genotyping for variants that increase risk of type 1 or type 2 diabetes or other diseases that may increase the risk of CVD, and genotyping for risk loci that alter cholesterol and lipid profiles. Genetic counselors may also help in the area of pharmacogenomics. An example would be genetic testing for safety measures with Coumadin, the most commonly prescribed anticoagulant for the treatment and prevention of thromboembolic events. The FDA-approved genetic test is a safety measure to reduce the adverse events associated with this therapy. The commercially available tests assess genetic variation in the genes cytochrome P450 2C9 (CYP2C9). Up to 35% of the population inherits a form of CYP2C9 that results in CYP2C9 enzyme deficiency. This results in a buildup of Coumadin in the body and increases the risk of bleeding. The genetic tests also assess inherited differences in the gene vitamin K epoxide reductase complex subunit 1 (VKORC1). Coumadin/ warfarin works by inhibiting active clotting factors. It does this by suppressing VKORC1. Genetic differences in VKORC1 alter the dosing of warfarin necessary to inhibit VKORC1. Thus, in sum, a recommendation for lower doses of warfarin would be given to patients with genetic variants in VKORC1 and/or CYP2C9.

The research Program in Translational Genomics can be divided into two main areas: collecting DNA for a biorepository to link genetic information with phenotypic information, and discovery research that involves identifying new structural variation in the genome that is linked with clinical disease. A foundation of this research component is a strong bioinformatics core that is able to extract data from electronic medical records and other sources into a registry and database that can be shared between institutions, track these patients and add follow-up data, and analyze gene expression data, SNP data, and other analysis tools.

DNA can be isolated from blood or saliva (buccal samples) and stored in a repository. DNA isolation from tissues, including the heart, vessels, or other tissues, may also be considered. DNA is routinely stored at −20°C or −80°C. Automation increases the efficiency in DNA isolation and should be weighed as an option when outlining needs for a core. Several options exist on the market. A bar coding system is recommended to meet HIPAA requirements for de-identified samples.

A discovery research arm of a translational research program is driven by the quality of the scientists within the program. Opportunities abound in several areas, including single-gene disorders, complex disease, and congenital heart disease. Depending on the area(s) of research and the background of the scientist, the resources/equipment needs will change. Fine mapping may be required to sequence areas of the genome that are suspected of harboring structural variation that are associated with altered cardiovascular phenotypes. Model organisms may be needed to determine if the genetic variation is sufficient to cause a change in phenotype.

In summary, imagine programs in translational genomics as standard of care for a medical center or academic institu-

tion. We can offer patients this level of care and commitment. Offering this level of care will bring new challenges and new insight into health and disease.

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