

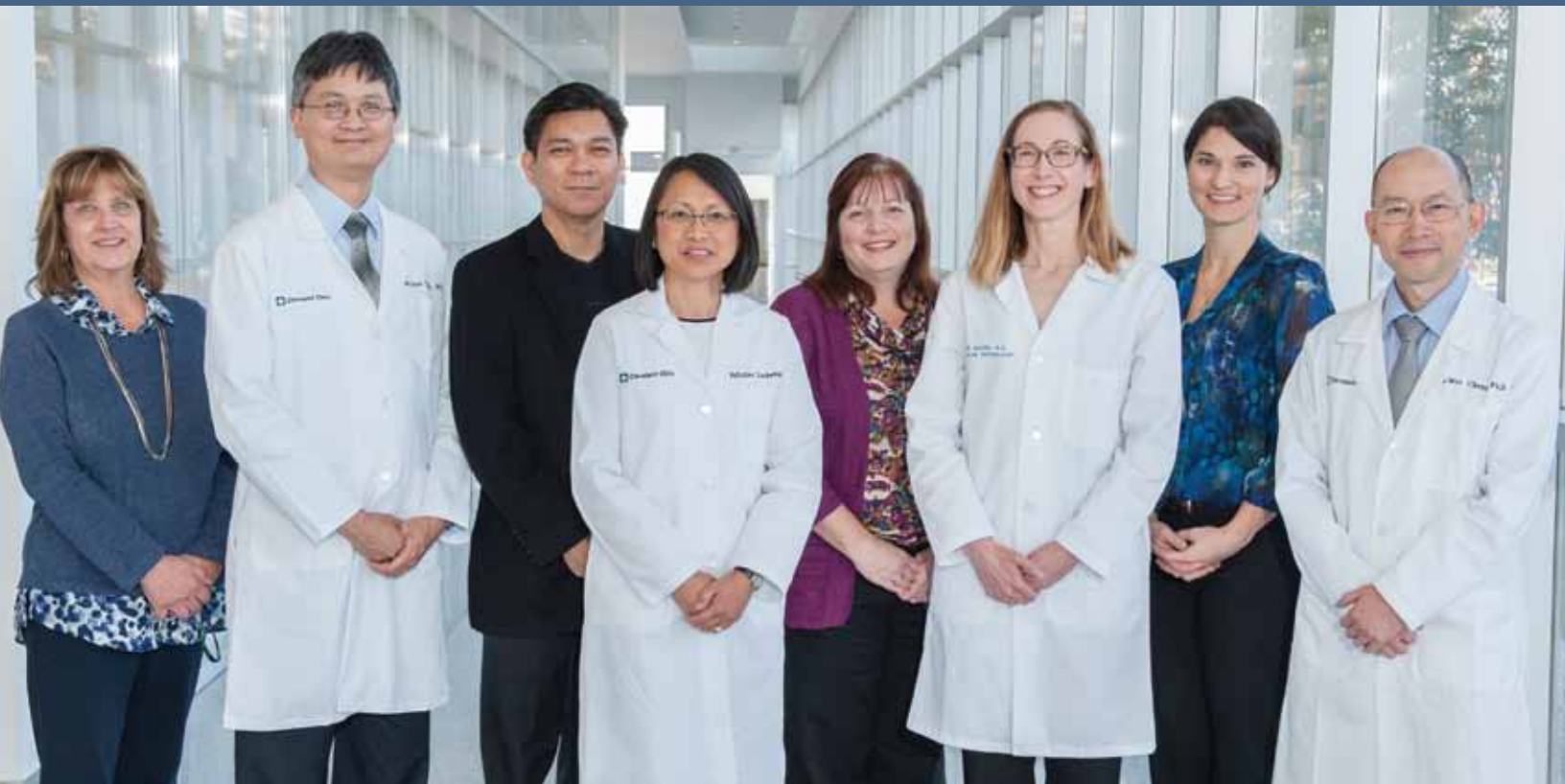


Cleveland Clinic
Robert J. Tomsich Pathology &
Laboratory Medicine Institute

Clinical and Translational

Pathology Innovations

A Publication of the Robert J. Tomsich Pathology & Laboratory Medicine Institute | Winter 2014



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What Responsible Next-Generation Sequencing May Bring

By Felicitas L. Lacbawan, MD

Next-generation sequencing (NGS) allows each nucleotide base in the genome to be read ten to a thousand-fold to identify variant change(s) in a particular gene that may be disease-causing. In contrast to Sanger sequencing, genes or regions of interest within the genome can be interrogated simultaneously in a high throughput mode by this massive parallel sequencing method. Without a doubt NGS propelled the translation of molecular diagnosis from bench to bedside, with whole exome sequencing (WES) and multi-gene panels becoming standard of care in clinical genetics and medicine. As this paradigm shift in genetic and genomic testing continues to unfold, demand for value- and evidence-based health care system intensifies. Hence, the push for responsibly designed NGS test panels in institutions like Cleveland Clinic.

NGS and its Limitations

Fundamental to NGS is the most critical preparation of the sequencing library that defines the sequences to be analyzed in the bioinformatics pipeline. This influences the generation of variant calls for eventual clinical interpretation. Diagnostic yield is dependent on several factors and foremost is the design of the library and its proper preparation. This includes the enrichment method used in the preparation of the sequencing library, the exome coverage or total number of exons of targeted genes in the panel, the depth of coverage, and the need to gap fill by Sanger sequencing. NGS is not optimal in the presence of homopolymers, triplet repeats, structural variants, GC-rich, and homologous regions or pseudogenes complicating library design. The number of allele drop-out, copy-number variant detection limit and false positivity are not to be overlooked. The variant filtering threshold and observed variant frequency in the analytic pipeline also do matter. In calling the variants, there may be ambiguity of gene variant assignments and off-tangent variants. Reliance on various existing databases including the Human Genome Mutation Database, Online Mendelian Inheritance for Man and ClinVar and (manual) literature

review of newly published genes to come up with acceptable clinical interpretation for a variant identified still remains. Though recently there is an increasing number of clinically more defined variants, variants of unknown significance (VUS) can be challenging. Inherent in the technology is the fact that sensitivity plateaus with an increasing number of exons or genes being sequenced. Clearly, familiarity of the genes together with the knowledge of the limitations of the sequencing technology and the bioinformatics pipeline employed are prerequisites to the design of a targeted NGS panel, be it disease-focused or laboratory-specific.

WES Experience to Date

In the past few years we witnessed the blurring of the line drawn between translational research and clinical testing with the use of WES that ended diagnostic odysseys or led to life-saving treatment of patients. WES interrogates coding regions (exons) of thousands of genes simultaneously. The sequences generated are compared to normal reference sequences to identify any variants in the patient. All variants go through filters and compared with known variants in established databases to determine pathogenic classification of the base change in the gene. Inheritance pattern and phenotype are reviewed to correlate with the identified variants. WES claims a diagnostic yield of 25% in 2,000 consecutive cases with or without neurologic disorder and improved to 31% in trio sequencing that includes both parents of proband.¹ Diagnostic yield varies among clinical phenotypes, specific neurologic (36.1%), neurologic (27.2%), neurologic plus other organ system (24.6%) and non-neurologic (20.1%). About 30% of the positive cases harbored variants in previously reported disease genes. Incidental findings unrelated to clinical condition, besides carrier status for recessive conditions, demand closer attention. Almost 5% of cases had medically actionable incidental findings in genes unrelated to the phenotype, including 3% with variants in the 56 genes recommended

On the Cover: The PLMI NGS Team and Clinical Collaborators (l to r) are Carol Hren, PLMI Center for Pathology Informatics; Wilson Tang, MD, Cardiologist, Heart & Vascular Institute; Hubert Fernandez, MD, Neurologist, Neurological Institute; Felicitas Lacbawan, MD, Section Head, Molecular Pathology; Maureen Jakubowski, NGS Development Technologist; Laurie Bauer, DO, MS, MGP Fellow; Jackie Riley, MS, Laboratory Genetic Counselor; and Yu-Wei Cheng, PhD, Technical Core Director, Molecular Pathology. (Not in photo: Rocio Moran, MD, Genomic Medicine Institute.)

for reporting by the American College of Medical Genetics and Genomics.^{1,2} Of the disease-causing variants in this patient cohort, more than half are novel and almost a third are variants in genes that had only been described very recently. It is expected that discoveries of new genes will increase the rate of diagnosis using NGS but the disease-causing variants in the noncoding regions of the genome will remain undetected by WES. There are advantages of trio sequencing in the identification of *de novo* and compound heterozygous variants as demonstrated in this study, though non-paternity may be unveiled. Because of the psychosocial implications of variants uncovered by WES, extensive genetic counseling before and after testing is paramount.

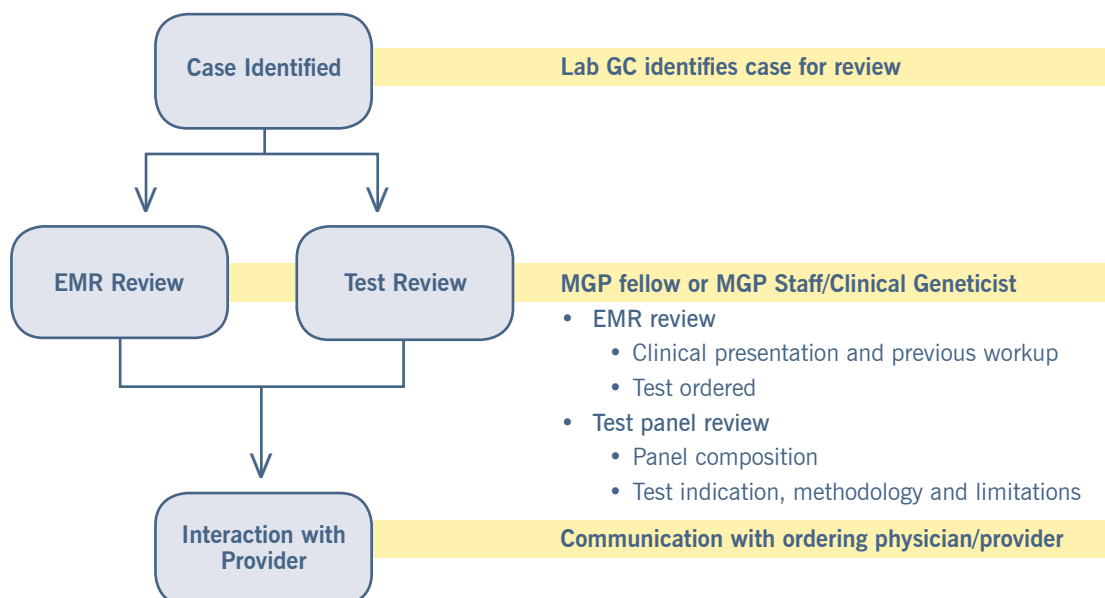
Against the backdrop of improving techniques in NGS, the debate continues on whether to use WES instead of gene panels for a patient with an underlying genetic cause. Though WES is comprehensive, the cost (\$8,000 to \$15,000) and the presence of poorly covered exome regions, as well as the burden of incidental findings and VUS, remain as drawbacks. It is clear however that the choice depends on the patient's phenotype and the differential diagnosis being considered. There are 14,741 genes described but only 4,274 of described phenotypes have known molecular basis and 1,682 phenotypes remain with no molecular basis (<http://omim.org/statistics/entry> accessed 11/3/2014 OMIM) based on the Online Mendelian Inheritance in Man Entry Statistics. This

supports the clinical use of targeted gene panels, at least for now. They are usually more focused or disease-specific and consequently the rate of molecular diagnosis is greater, in contrast to WES. In addition, there is less bioinformatics load in the analysis of targeted gene panels and as a consequence, lesser incidental findings. The group at Baylor College of Medicine shared the same experience with their mitochondrial genome sequencing where the yield was 10% more sensitive than WES. Further studies on WES diagnostic yield and clinical utility are ongoing in another academic institution.

Designing Cleveland Clinic Targeted NGS Panels

Traditional test utilization management is being challenged by the availability of NGS gene panels not only to clinical geneticists but to any clinician. Accessibility of NGS platforms enables laboratories to design and make clinically available their own multiplex gene panels that may be disorder-centric or laboratory-specific. These panels however still cost more, in some instances even more expensive than WES. Some NGS panels are not dictated by utility and unfortunately promote a “shot-gun” approach to molecular diagnosis by some clinicians. To address these concerns, the Section of Molecular Pathology at the Robert J. Tomsich Pathology and Laboratory Medicine Institute has initiated a Genetics and Genomics Test Review (GGTR) as part of its test utilization management program³ (see diagram). Molecular tests ordered by clinicians are monitored and reviewed daily through a

Genetic and Genomic Test Review Process



pending log of molecular send-outs by the laboratory genetic counselor. Each gene panel test ordered is assessed as to the gene composition of the panel, the indication of testing vis-à-vis the patient's clinical findings and previous laboratory work-up, the relevance of the results in the patient's treatment management, and the limitations of test methodology. This process is coupled with a monthly review of all molecular send-outs collated from the "miscellaneous XTUBE" send-out orders. The total volume of each molecular test is tallied and provides a basis for the targeted gene panel design and development. Furthermore, test result interpretation and qualification of reported VUS are also serviced by our Section. Coupled with end user feedback on test utilization, we develop clinical testing algorithms with clinical practice groups, such as neurology (see companion article on Spinocerebellar ataxia on page 7). We hope to determine detection rate and establish evidence-based test utilization that will later influence test panel iteration or development. As most of these gene panels are laboratory-developed tests and with the latest Food and Drug Administration draft of the framework guidance and notification and medical device reporting for LDTs, the need for laboratory experts working with clinicians within the institution is underscored.

The HeartGENE Panel

Given the merits of targeted NGS panel testing, the most appropriate resource and expertise, the laboratory workflow and test turn-around time we currently have, the results of test utilization reviews, and the continuing effort to draw collaboration with clinicians, we designed our HeartGENE panel. The panel covers at least 50 genes for aortopathy, cardiomyopathy and vasculopathy. Its composition is dictated by its clinical utility and frequency of test orders in our institution, the No. 1 heart program in the nation for 20 consecutive years. Clinical utility is based on clinicians' input on how often the test will be ordered, the impact of the result on the clinical or surgical management of the patient and the published literature about the disorders and the genes. Technical considerations include the design of the library, specifically the topography and frequency of common clinically relevant variants and the library preparation methodology that allows sufficient coverage of the regions harboring these variants. Coupling variant calls with clinical data are not easily scalable without automation. However,

working with cardiology and genetic expert colleagues will facilitate arriving at meaningful interpretations.

To better illustrate how clinical utility influences our NGS gene panel design and development, thoracic aneurysm and dissection is discussed here. Aortic aneurysms and dissections with an incidence of 10.4 per 100,000 persons rank as the 15th major cause of death in the U.S. and account for 1-2% of all deaths in Western countries. Thoracic aortic aneurysm and dissection (TAAD) can occur sporadically, as a part of a syndrome (Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome vascular type and others) or as nonsyndromic but familial. About 20% of nonsyndromic patients with thoracic aortic disease have a first-degree relative with a similar condition. This familial thoracic aortic aneurysm and aortic dissection (FTAAD) often occurs in an autosomal dominant with variable expression and decreased penetrance, but with earlier onset of disease when compared to sporadic thoracic aortic disease. With medial degeneration as an underlying pathology of thoracic aortic disease, disruption of one or more elements of the cytoskeletal-receptor-extracellular matrix related to the vascular smooth muscle cells of the thoracic aorta is thought to result in these TAA with underlying genetic etiology. Mutations in *ACTA2*, *TGFBR1*, *TGFBR2*, *SMAD3*, *MYH11*, *MYLK* and *FBN1* genes are involved in this pathological process, accounting for 20% of the patients with FTAAD.^{4,5,6}

Marfan syndrome (MFS) is the most well-known of the syndromes associated with TAAD, and is caused by mutations in *FBN1* gene. MFS is a clinical diagnosis based on the characteristic connective tissue manifestation and on family history, using the revised Ghent nosology. Based on the accuracy of clinical diagnosis, the mutation involved and the testing methodology used, mutation detection in *FBN1* ranges from 70-93%.⁸ *FBN1* mutations have also been rarely associated with FTAAD when patients do not fulfill the criteria for MFS. The vascular form of Ehlers-Danlos syndrome (EDS) is type IV characterized by rupture of arteries, uterus and intestines along with facial and musculoskeletal features. EDS type IV is also associated with TAAD. Clinical criteria have been suggested and diagnosis can be confirmed by genetic testing of *COL3A1*. More than 95% of patients with Loeys-Dietz syndrome (LDS) have TAAD and may have underlying mutation of *TGFBR1*, *TGFBR2*, *SMAD3* and *TGFB2*, listed by the order of frequency. Since minimal clinical diagnostic criteria do not exist, genetic testing plays an important role in

the diagnosis of these patients. It has been suggested that all the four genes involved with LDS in patients with a characteristic triad (widely spaced eyes, cleft palate/bifid uvula and aortic/arterial aneurysms/tortuosity), Marfan-like phenotype, vascular Ehlers-Danlos-like phenotype, other cardiac abnormalities (ASD,VSD,PDA) and precocious TAAD be sequenced.⁷

Since thoracic aortic disease is usually asymptomatic until an acute complication occurs and because it is best treated in the quiescent state, early recognition is of dire importance.⁹ Only a few genotype-phenotype correlations have been delineated so far in patients with FTAAD and gene mutations. These are limited to the association of iris flocculi, livedo reticularis, coronary artery disease and cerebrovascular disease with *ACTA2* mutations, patent ductus arteriosus with *MYH11* mutations and increased risk of aneurysms and dissections in other vessels with *TGFBR2* mutations. Hence, sequential genetic testing strategies, as in testing for the common *ACTA2* as first step followed by other genes and also multi-gene panel in which all known associated genes are sequenced as a first step have been advocated.^{4,9} Clearly, genetic testing plays an important role in patients with TAAD in the evaluation, surgical management and screening for co-existing non-aortic vascular complications. Only those relatives carrying the same mutation in one of the genes causing TAAD in the proband would need routine medical screening and interventions.⁹ Guidelines for initial evaluation and surveillance imaging have been set forth for patients with Marfan's syndrome⁹, LDS¹⁰ and in patients with confirmed mutations of (*TGFBR1*, *TGFBR2*, *FBN1*, *ACTA2*, or *MYH11*).⁹ Screening for non-aortic vascular disease may be pertinent, such as cerebrovascular disease in patients with *ACTA2* mutations⁴ and in patients with LDS.⁹ Earlier surgical management has been recommended in patients with specific genetic mutations⁹, for example, aortic root surgery for adults with mutations in *TGFBR1*, *TRFBR2* and *SMAD3*, and an aortic root dimension greater than 4 cm or having a greater than 0.5 cm increase in aortic root dimension within one year.¹⁰ As more genetic and clinical predictors distinguish those at risk for dissection at smaller aortic diameter, there will be better justification for earlier surgical intervention to prevent dissection.

After we launch this HeartGENE panel, a prospective study on diagnostic yield and outcome of intervention will be

undertaken. This will guide us in the development of clinical testing algorithm(s) and possibly improve the design and utilization of this gene panel. We hope to highlight the effects on our test utilization management and provide a glimpse of the economies of genetic and genomics testing for this group of disorders. As we continue to navigate the current molecular landscape and address today's key molecular diagnostic challenges, we offer our insights in the design of our NGS panel, the rationale behind its development, and a sense of how actionable results will be used in clinical care.

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About the Author

Felicitas L. Lacbawan, MD, FCAP, FACMG



Felicitas L. Lacbawan, MD, FCAP, FACMG, has served as the Head of the Section of Molecular Pathology, Department of Laboratory Medicine, Robert J Tomsich Pathology and Laboratory Medicine Institute, since May 2014. The integrated laboratories of Molecular Pathology cover the sub-disciplines of Cytogenomics,

Molecular Genetics and Genomics, Molecular Hematopathology and Molecular Oncology and provide chromosomal and molecular diagnostic tests for various constitutional disorders, cancer and pharmacogenomics. Dr. Lacbawan is the founding Program Director for the Molecular Genetic Pathology Fellowship at Cleveland Clinic.

Dr. Lacbawan received her undergraduate and medical degrees from the University of the Philippines (UP) and became a faculty member of the Department of Human Biochemistry and Molecular Biology at the UP College of Medicine. She served her clinical and anatomic pathology residency at SUNY Upstate Medical University and her fellowship in clinical genetics at the National Human Genome Research Institute, National Institutes of Health (NHGRI-NIH). She is board certified in clinical pathology, anatomic pathology, clinical genetics and molecular genetic pathology. She has

previously worked at the Medical Genetics Branch, NHGRI-NIH, Children's National Medical Center (CNMC), Lombardi Cancer Center at Georgetown University Medical Center (GUMC) and SUNY-Downstate Medical Center in various capacities as a clinical geneticist and a molecular genetic pathologist. She was a member of the faculty at the George Washington University School of Medicine and Health Sciences, the Georgetown University School of Medicine and at the SUNY Downstate College of Medicine as a Clinical Professor.

Dr. Lacbawan was a recipient of the Interagency Personnel Agreement between CNMC and NHGRI-NIH for five years. She was the founding Director of the CLIA-certified molecular diagnostic laboratory at the Medical Genetics Branch, NHGRI and the NYSDOH-certified molecular pathology laboratory at SUNY-DMC. She is currently a member of the College of American Pathologists (CAP) Subcommittee on Biochemical and Molecular Genetics, CAP Subcommittee on Pharmacogenomics and the American College of Medical Genetics Professional and Practice Guidelines Committee, and also serves as a special volunteer at the Undiagnosed Disorders Program at the NHGRI-NIH. Her publications are on various developmental, mitochondrial and neurological genetic disorders, chromosomal anomalies, and molecular genetic test proficiency and test utilization.

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Testing Algorithm for Spinocerebellar Ataxias

By Laurie Bauer, MD, Jacquelyn Riley, MS, Hubert Fernandez, MD, Felicitas L. Lachawan, MD

With increasing focus on value-based healthcare and more options for testing and evaluating patients than ever before, Cleveland Clinic had implemented several utilization management (UM) strategies to optimize laboratory test ordering practices among our clinicians. Genetic testing in particular has been a priority for our UM initiatives. Though relatively low in volume, genetic tests represent significant cost to our institution. Additionally, the rarity of many genetic conditions and the rapid advancements in new testing methodologies contribute to the complexity of genetic testing and makes it especially vulnerable to inappropriate utilization. An offshoot of the Genetics Genomics Test Review initiative that has addressed concerns around both cost and complexity is collaborating with clinician specialists in the development of genetic testing algorithms.

Testing algorithms provide guidance to clinicians pursuing genetic diagnosis by incorporating the patient's clinical and family histories. In addition, algorithms target more common etiologies first and consider the clinical sensitivity and utility of available tests. These approaches facilitate the diagnosis in the most timely and cost-effective manner and standardize the approach to care across multiple providers in a group practice setting. It also allows the monitoring of test ordering practices that may reflect evidence-based testing.

Our institution's test UM team partnered with the Section of Movement Disorders in the Neurological Institute to develop such an algorithm for spinocerebellar ataxias. Spinocerebellar ataxia (SCA) is a neuromuscular disorder involving degeneration of the cerebellum or spinal cord. The incidence of hereditary forms varies by population but is estimated to be around 1-9 per 100,000. More than 100 different genes have been associated with various types of SCA, though many are quite rare. In addition, acquired causes (e.g., ethanol, vitamin deficiency, multiple sclerosis, vascular disease, tumors and paraneoplastic disease) of ataxias must be distinguished from genetic causes in order to facilitate treatment and genetic counseling. If an acquired cause is discovered, costly genetic testing can be avoided. Late onset hereditary ataxias usually

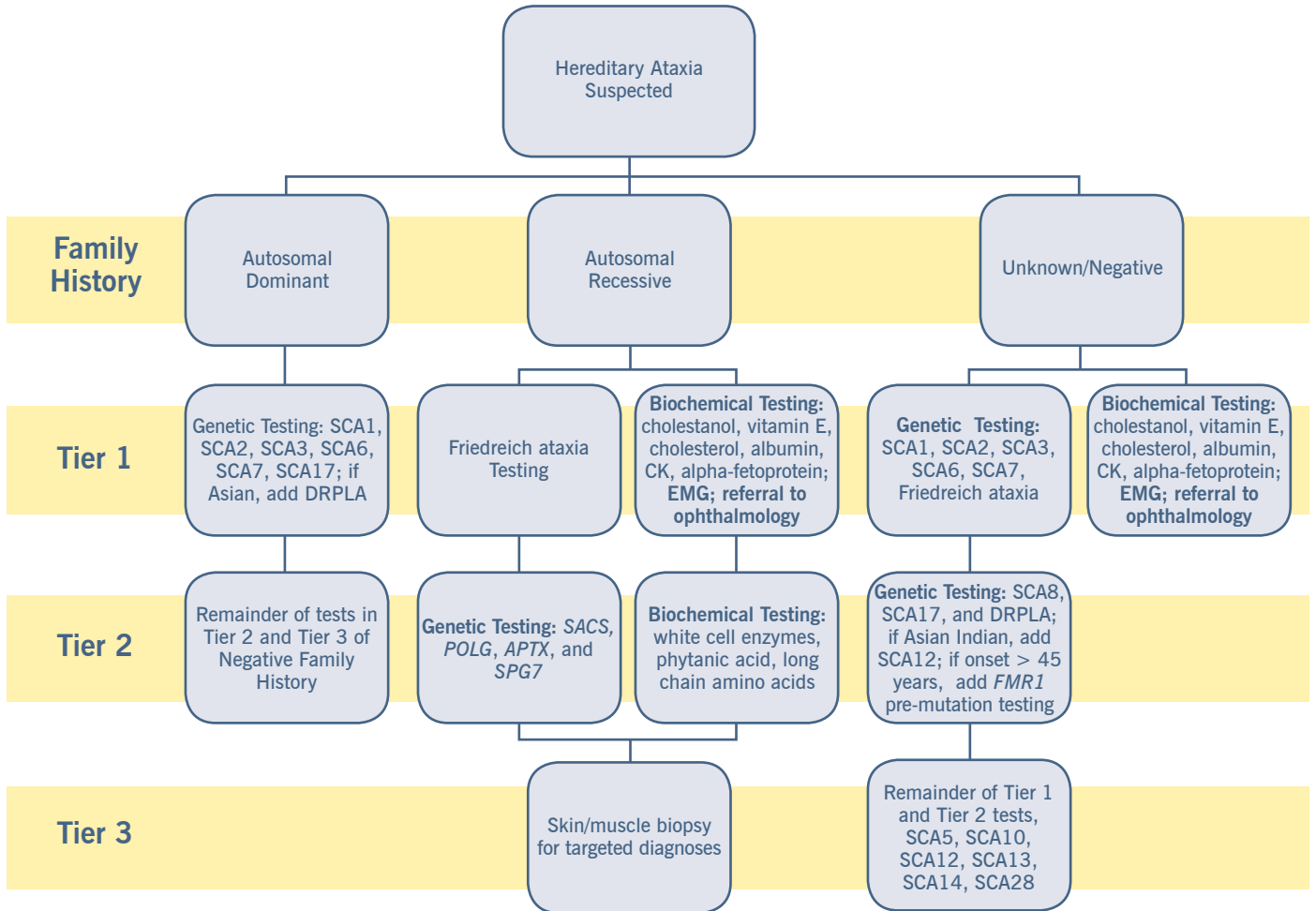
have a slowly progressive course and may have an autosomal dominant, autosomal recessive, X-linked, or mitochondrial mode of inheritance. With few exceptions the hereditodegenerative ataxias have only symptomatic treatment. For example, autosomal recessive ataxia with vitamin E deficiency can be treated with lifelong oral high-dose vitamin E to slow or reverse symptoms.

The European Federation of Neurological Societies (EFNS) and the European Neurological Society (ENS) recently published a joint consensus statement on the diagnosis and management of chronic ataxias in adulthood, focusing on the hereditodegenerative ataxias. Utilizing these recommendations, and in collaboration with our neurology colleagues, we constructed an efficient algorithm to guide diagnosis of these ataxias. The diagnostic strategy utilizes medical history (including a detailed family history), race/ethnic background, imaging, physical examination, laboratory testing and molecular genetic testing. Neuroimaging is paramount in the diagnosis and should be performed before any molecular genetic testing in order to rule out other etiologies that would obviate the need for complicated molecular genetic testing. Furthermore, neuroimaging may help guide genetic or other testing.

A detailed personal and family history should be elicited, with particular focus on relatives with movement disorders, but also including any other neurological and even non-neurological problems. The type of hereditodegenerative ataxia varies based upon geographic location. Therefore, documenting the patient's country of origin and race/ethnicity can guide the testing strategy. The worldwide distribution shows SCA3 (21%), SCA2 (15%), SCA6 (15%), SCA1 (6%), SCA7 (5%) and SCA8 (3%) to be the most common types. The distribution is similar in the United States except for SCA8 being less common.

Results of brain MRI and physical exam, along with the patient's clinical and family histories, will guide the next step. If a genetic etiology is suspected, the genetic testing algorithm

Figure 1



can guide the selection of genes (figure 1). Testing should proceed to tier 2 and tier 3 testing only when all previous evaluations are non-diagnostic and suspicion of a genetic cause remains high. Unfortunately, approximately 50 percent of patients who undergo genetic testing will ultimately have no definitive diagnosis, but such testing may be beneficial for those patients with improper diagnoses such as multiple sclerosis, Parkinson disease and Huntington disease. Please refer to table 1 for features of the most common SCAs.

For the most common SCAs (with triplet repeats), the test methodology usually involves PCR bracketing triplet repeat regions followed by fragment size analysis using fluorescent capillary electrophoresis. Large Next Generation Sequencing (NGS) panels sequencing hundreds of genes are available,

but it is best to begin with a panel of the most common repeat expansions due to the limitations of NGS to sequence areas with extensive repeats.

Given the need to deliver high quality care for lower cost in our evolving healthcare system, appropriate utilization of resources is critical. Our institution is implementing diagnostic genetic testing algorithms, along with other UM strategies, to help clinicians optimize their use of these costly and esoteric tests. We believe this approach promotes timely and accurate diagnosis for improved patient care in a cost-effective manner. As we gather follow-up data on the use of the genetic test algorithms in our institution, our goal is to review outcomes data with clinicians to further refine algorithms for our patient population and establish evidence-based test ordering.

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Disorder	Gene	Mutation	Selected Distinctive Characteristics	Age of Onset
SCA1	<i>ATXN1</i>	AD, CAG repeat	Pyramidal signs, peripheral neuropathy, occasional cognitive decline	Early childhood to late adult
SCA2	<i>ATXN2</i>	AD, CAG repeat	Cuba, Korea, dysarthria, dementia, slow saccades, and peripheral neuropathy	Early childhood to late adult
SCA3	<i>ATXN3</i>	AD, CAG repeat	Portugal, Brazil, lid retraction and infrequent blinking, ophthalmoplegia, impaired speech and swallowing	Early childhood to late adult
SCA6	<i>CACNA1A</i>	AD, CAG repeat	Japan, mild disease, presents as a "pure" cerebellar ataxia with dysarthria and gaze-evoked nystagmus	Mid to late adult
SCA7	<i>ATXN7</i>	AD, CAG repeat	Retinal degeneration, ophthalmoplegia	Early childhood to late adult
SCA17	<i>TBP</i>	AD, CAG repeat	Japan, widespread cerebral and cerebellar dysfunction, dementia, psychiatric symptoms	Early childhood to late adult
SCA8	<i>ATXN8OS</i>	AD, CAG/CTG repeat	Finland, gait and limb ataxia with abnormalities of swallowing, speech, eye movements	Early childhood to late adult
SCA12	<i>PPP2R2B</i>	AD, CAG repeat	India, Germany, China, action tremor of the arms followed by head tremor, ataxia, and occasionally bradykinesia and sensory neuropathy	Childhood to adult
DRPLA	<i>ATN1</i>	AD, CAG repeat	Japan, choreoathetosis, dementia, seizures, myoclonus, dystonia, mimics HD	Early childhood to late adult
FXTAS	<i>FMR1</i>	X-linked	Tremor, executive function defects, often have fragile X family history	Late adult
ARSACS	<i>SACS</i>	AR, indel, missense	Spasticity, severe neuropathy	Early childhood to young adult
FRDA	<i>FXN</i>	AR, GAA repeat expansion, indel, missense, nonsense, splice	Mixed cerebellar/sensory ataxia, scoliosis, areflexia, pyramidal weakness, extensor plantar responses, HCM	Early childhood to young adult
AOA1	<i>APTX</i>	AR, indel, missense	Japan, Portugal, sensorimotor neuropathy, chorea, cognitive impairment	Childhood
SP7	<i>SPG7</i>	AR, compound heterozygous, rare AD	Progressive weakness/spasticity of lower limbs, pure and complicated phenotypes possible	Childhood to late adult
ANS	<i>POLG</i>	AR, missense	Mitochondrial, Europe, ophthalmoplegia, neuropathy, myoclonus, dystonia, encephalopathy, Parkinsonism	Early childhood to adult

Table 1: Features of selected heredodegenerative ataxias

Abbreviations: AR-autosomal recessive; AD-autosomal dominant; SCA-Spinocerebellar Ataxia; DRPLA-dentatorubral-pallidoluysian atrophy; HD-Huntington disease; FXTAS-fragile X-associated tremor ataxia syndrome; ARSACS-autosomal recessive spastic ataxia of Charlevoix-Saguenay; FRDA-Friedreich's ataxia; AOA1-ataxia with oculomotor apraxia type 1; SP7-spastic paraplegia 7, autosomal recessive; HCM-hypertrophic cardiomyopathy; ANS-ataxia neuropathy spectrum [note that this includes conditions formerly known as MIRAS (mitochondrial recessive ataxia syndrome) and SANDO (sensory ataxia neuropathy dysarthria and ophthalmoplegia)].

Training the next generation of pathologists in Rwanda

Pathologist takes opportunity to teach in reinvented country



Carol Farver, MD, MS

Rwanda has made significant strides in improving the health care of its citizens since the 1994 genocide in Rwanda destroyed much of the socio-economic fabric of country as well as its health infrastructure. But, as Carol Farver, MD, MS, a staff pathologist in the Department of Anatomic Pathology, found out, the healthcare

system still remains inadequate for the Rwandan's 12 million citizens.

Dr. Farver and her husband, Robert Needlman, MD, a practicing pediatrician, visited Rwanda in August as part of the Clinton Global Initiative – Human Resources for Health program. Dr. Farver had the opportunity to teach residents enrolled in Rwanda's first pathology residency program at the University Hospital of Kigali. She also did clinical work at other referral hospitals in Kigali, Rwanda's capital and largest city with 1 million people, and at Rwanda's most modern hospital in Butaro, built in the mountainous north to serve the rural poor.

"It's an amazing country," says Dr. Farver. "They have come a long way in a short time. They are doing all the right things." She gives much of the credit to Rwanda's leadership, particularly President Paul Kagame and the country's health minister, Agnes Binagwaho, for their efforts to improve health care.

In the early 1990s, Rwanda had the lowest life expectancy of any country in the world. Rates of preventable deaths due to infectious disease and unsafe birth soared as a result of the 1994 genocide. In addition, workforce setbacks plagued the country and many clinicians fled or were killed.

Over the last ten years, Rwanda's health system development has led to the most dramatic health improvements in history. Deaths due to infectious disease and maternal disorders have declined dramatically since 2000, and Rwanda is now on track to achieve each of the health targets set by the United Nations Millennium Development Goals (MDGs) for

child and maternal mortality, HIV infection, tuberculosis and malaria. Between 2000 and 2011, life expectancy in Rwanda rose from 48 to 63 years of age (up from just 27 years of age in the early 1990s). Rwanda has also achieved 100 percent vaccination of its children and has implemented an HPV vaccination program that has inoculated more than 80 percent of teenage girls. By comparison, only a third of girls aged 13-17 in the U.S. have been fully vaccinated.

In turn, these advances bolstered Rwanda's economic growth and are helping to lift millions from poverty. In the wake of the genocide that killed nearly one million people, such a turnaround seemed nearly impossible.

Much of the credit for the turnaround belongs to the government of Rwanda's centralized planning. In 2000, the Rwandan government created a plan, called Vision 2020, to develop economically into a middle-income country over the next two decades. Improving health was key to development and alleviating poverty. "Rwanda has made sure that the poorest and most vulnerable have health benefits," says Dr. Farver.

As part of their efforts, volunteer providers, nurses and community health workers go into their neighborhoods to look for early signs of disease and illness. Nearly all Rwandans now have health insurance, and the poorest 25 percent of the population pay no fees. The average health care cost is \$56 per person per year.

In 2002, the Ministry of Health asked the Clinton Health Access Initiative — an organization that first came to Rwanda to assist the government in the planning of its response to HIV and AIDS — to extend invitations to leading universities and academic medical centers from across the United States for the establishment of an academic consortium.

One of the leading organizations providing assistance is Partners in Health (PIH), which has strengthened Rwanda's public health system in three rural districts through three hospitals and 41 health centers to bring the benefits of modern medical science to those most in need. PIH draws on the resources of the world's leading medical and academic institutions.

In addition, the Human Resources for Health Program was developed by the Rwandan Ministry of Health in partnership with U.S. medical schools to support the development of



The “hard-working and incredibly eager” pathology residents in Rwanda.

critically needed clinical, teaching and research skills of current and future Rwandan faculty and specialist physicians (including pathologists) to meet patient care needs at the country’s hospitals.

The Human Resources for Health Program focuses on knowledge transfer, sustained collaboration and the establishment of new medical residency, nursing specialty, health management, and oral health programs within the Rwandan education system. Dr. Farver and her husband were among the U.S. subspecialist physicians who participated in the program. American faculty returning to their home institutions after participating in the program continue to play an integral role in strengthening curricula.

While Rwanda has made great strides, it still has a severe shortage of doctors, specialists and other healthcare workers, says Dr. Farver. One key cause is the lack of faculty to train future physicians. To meet the country’s needs for pathologists and pathology training programs, Rwanda’s Medical School created a curriculum for a new pathology program that began in January 2013. The program sends pathologists to Rwanda to teach and will bring Rwandan medical students to train in the United States. In addition, the Human Resources for Health Program is working to adequately equip health facilities to ensure proper teaching environments.

Dr. Farver spent a month training these new residents in pathology. “The pathology residents that I worked with were amazing – hard-working and incredibly eager students, but they had little material from which to learn.” In an effort to overcome this, Dr. Farver took over a virtual slide library of more than 1,500 pathology cases on a portal hard drive supplied by the PLMI ePath group, under the direction of Thomas Bauer, MD, PhD.

In addition, live teleconference lectures were delivered by faculty in their offices at Cleveland Clinic to the Rwandan residents in their classrooms. Jennifer Brainard, MD, (cytology) and Deepa Patil, MD, (gastrointestinal pathology) delivered a total of seven lectures. “We want to continue to do the teleconferences on a regular basis,” says Dr. Farver. “They are so eager to learn. We want to maintain this relationship.”

Despite the media stories of failing states and civil wars in the developing world, the re-invention of Rwanda offers hope. “The rest of the world – wealthy countries as well as poor – can learn from Rwanda’s rise,” Dr. Farver says.

Pathology Innovations Magazine offers information from the medical staff in the Cleveland Clinic's Robert J. Tomsich Pathology & Laboratory Medicine Institute about its research, services and laboratory technology.

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Alumni Connect

Dear Alumnus,

This is the second edition of our commitment to provide you with regular alumni communication. As noted previously, exciting educational activities are happening within RT-PLMI. With every correspondence, we will provide information on upcoming conferences, educational events and publications. This issue of Pathology Innovations is one of several important initiatives highlighting our scientific updates.

Article of the Week

You will be receiving the "Article of the Week" in the near future by email. This educational activity, now in its 100th week, highlights recent seminal articles, reviews or practice-changing updates. These articles are mailed to all our residents, faculty and affiliates, and will now include our esteemed alumni. This initiative has been well-received as part of keeping up with emerging literature, general education and sharing of relevant information. Please give us your feedback and we encourage you to contribute future articles that would be of educational interest to your colleagues.

L Building Renovations to increase efficiency, productivity and capacity

RT-PLMI began extensive renovations to the L Building earlier this year to increase efficiency, productivity and capacity for the clinical laboratories. Over the past year, new automated chemistry lines have been installed. Hematopathology, including manual hematology laboratories, has moved from the first floor to the newly renovated third floor. The first floor will be the site of a new Education Suite that will house all the residents, fellows, MT and Cytology Schools, a library with a multi-headed scope and a large conference room. Tissue procurement and banking will also be in a new area on the first floor. The second floor will have an expansion of the Cytology Laboratory, Digital Imaging and a renovated secretarial area. The project remains on time and budget, with an estimated completion date of 2015. In upcoming "Alumni Connect," we will include pictures of these projects. We do hope that you will have an opportunity to visit the department and see the amazing transformation.

We want to hear from you. Please send us your news and accomplishments to be featured in this "Alumni Connect" section in future issues of *Pathology Innovations*. If you prefer to receive an electronic version, please let us know by providing your preferred email address to ClientServices@ccf.org.

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The Cleveland Clinic Foundation
Pathology Innovations Magazine

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