Faculty of Clinical Sciences, College of Medicine, University of Lagos

15th Annual Scientific Conference and Gathering

5th Gathering Lecture

PRECISION MEDICINE: MOLECULAR DIAGNOSIS AND DIGITAL FACIAL ANALYSIS TECHNOLOGY APPLICATIONS IN CONGENITAL CARDIOVASCULAR DISORDERS.

Tuesday 10th July 2018

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PROTOCOL

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The Chairperson and members Faculty of Clinical Sciences Conference Committee
Previous Distinguished Gathering Speakers
Professors and all distinguished Colleagues in the Faculty of Clinical Sciences
Other members of the Academia
My Lords Spiritual and Temporal
Gentlemen and ladies of the Press
Ladies and Gentlemen.

PREAMBLE

I am grateful to Almighty God for giving me this priviledge to stand before you today. I thank the Dean, Faculty of Clinical Sciences, The Chairperson and members of the Faculty Gathering and Conference Committee for inviting me as the 2018 Faculty of Clinical Sciences Annual Gathering Speaker. The theme of our Conference this year is 'Harnessing local resources for Biomedical Engineering in Nigeria' while the sub-theme is 'Precision medicine in Diagnosis and Treatment'
I am delighted and honoured to speak to you on a topic closely related to the subtheme

PRECISION MEDICINE: MOLECULAR DIAGNOSIS AND DIGITAL FACIAL ANALYSIS TECHNOLOGY APPLICATIONS IN CONGENITAL CARDIOVASCULAR DISORDERS.

As I speak, I vividly recall an event that occurred during my house job. I was this young doctor, eager to learn and reproduce what I saw my seniors do. We had this child with a jaw swelling diagnosed with Burkitt's lymphoma and I had to be giving the cytotoxic medications.

Soon after that child was discharged, we had another patient come with a jaw swelling. I clerked and examined the patient with much excitement. Ready to show my very knowledgeable Registrar that I had stepped up in my diagnostic skill from the last experience. I boldly made a diagnosis of Burkitt's lymphoma. To my shock and dismay the Registrar on review of the case with me gently punctured my balloon by educating me that this one was not Burkitt's lymphoma but a jaw swelling from infection and only needed a course of antibiotics. Though I was deflated but I know it was great news for the parents since his diagnosis was certainly more welcome than mine.

Welcome to my baptism in medical diagnosis.
In this lecture, by way of an introduction I will discuss some aspects of the art and science of clinical medicine. Then, I will discuss key aspects of what we mean by precision medicine drawing heavily on my clinical work and research in paediatrics and paediatric cardiology. Finally, I will conclude by presenting a vision for precision medicine in Nigeria.

THE ART AND SCIENCE OF CLINICAL MEDICINE

Diagnosis is the traditional basis for decision-making in clinical practice. The science of diagnosis recognises the uncertainty clinicians face as they attempt to classify people with and without disease.[1] It is the vital engine that carries forward not only the train of treatment but also health outcomes.[2] It is a critical step in providing clinical solutions.
Clinical decision making has been described as a balancing act of art and science, intuition and analysis, gut instinct and evidence, experience and knowledge.[3] The patient has the best opportunity for a positive health outcome if diagnosis is accurate and early. In such a situation, clinical decision making will be tailored to a correct understanding of the patient's health problem.[4]

The earliest found documents on medical diagnosis is the Edwin Smith Papyrus, writings of Imhotep (3000-2630-BC) in Ancient Egypt.[5,6] This is the first document that presents a rational and scientific approach to medicine in which the conflict of medicine and magic is minimal. In it are written 48 cases of injury. For each case, the details of injury, examination of the patient, diagnosis and prognosis, and treatment are included. Subsequently, the use of empiricism, logic and rationality in the

diagnosis of an illness or disease was introduced in a Babylonian medical textbook, the Diagnostic Handbook written by Esagil-kin-apli (1069–1046 BC).[7] In the Yellow Emperor's Inner Canon (475-221 BC), Traditional Chinese Medicine, specified four diagnostic methods: inspection, auscultation-olfaction, interrogation, and palpation.[8]
Today, the diagnostic process is deemed to be a complex, patient centered, collaborative activity that involves information gathering and clinical reasoning with the goal of determining a patient's health problem. It occurs over time, within the context of a larger health care work system that influences the diagnostic process.[9]

In the diagnostic process, first, a patient experiences a health problem or, in the case of pediatric patients, parents observe the problem. They often choose at this point to engage with the health care system. For various reasons, this initial contact may be delayed in poor and middle-income countries like Nigeria. Once health care is sought, the process of information gathering, information integration and interpretation, and determining of a working diagnosis ensues. There are four types of information-gathering activities in the diagnostic process[9]

- Performing a clinical history and interview
- Conducting a physical exam
- Performing diagnostic testing
- Referring or consulting with other clinicians.

Obtaining an accurate history helps determine sequence of events which have led to the disease. It facilitates a more productive and efficient physical exam and the appropriate utilization of diagnostic testing.[10]

Adding physical examination to history taking helps the clinician refine the next steps in the process of diagnosis. Physical examination is the process of evaluating objective anatomic findings through the use of observation, palpation, percussion, and auscultation. When thoughtfully performed, physical examination is expected to yield 20% of the data necessary for patient diagnosis and management. [11]
A careful observation of overall appearance is important to identify malformations, especially the minor ones. Minor malformations are

physical variations that occur in less than 5% of the population, e.g., upslanting palpebrae, unusual ear helix, anteverted nares and other areas including the hands, genitalia and skin.[12] Table 1. On their own, they are usually of no clinical significance. However, when found with other malformations they may indicate an underlying syndrome.

Assessments of anthropometry, ectodermal features, skull, face shape and sections, hands and feet, joints and skeleton, genitalia and anus are vital in addition to organ system examinations. Unfortunately, for many individuals with malformations and/or an unusual appearance, with or without developmental delay, the history and examination do not suggest an immediate diagnosis and diagnostic testing is needed.

Table 1- A list of some minor anomalies that are used in syndrome delineation

Craniofacial	Other body areas	Skin
Sagittal fontanelleUpslanting palpebraeShort palpebraeAnteverted naresNata teethMalar underdevelopmentBifid uvulaPosteriorly rotated earsOpen metopic sutureBrushfield spotsOcular heterochromiaFlat philtrumHypoplasia anguli orisSingle central incisorMicrognathiaPreauricular pits or tagsMultiple hair whorlsEpicanthic foldsWide/close-spaced eyesLow nasal bridgeHypodontia	Bifid xiphoidUnusual umbilical position5th finger clinodactylyExcess nuchal skinSupernumerary nippleDeep sacral dimpleProminent heelsPectus excavatumUmbilical herniaSingle palmer creaseSingle umbilical arteryShawl scrotum	Hypopigmented patchesAplasia cutis congenitaVarious neviHairy patch on lower spineSebaceous nevusMild skin syndactylyCafé au lait spotsPigment streaking

The diagnostic process

Applying the brain-to-brain loop model, the diagnostic process can be described as having nine steps occurring in five phases. The steps are test selection and ordering, sample collection, patient identification, sample transportation, sample preparation, sample analysis, result reporting, result interpretation, and clinical action while the phases are pre-pre-analytic, pre-analytic, analytic, post-analytic, and post-post-analytic phases.[13] Laboratory medicine, anatomic pathology, and medical imaging are some of the important forms of diagnostic testing. [9]

Clinical reasoning and diagnosis

Usually, clinicians consider more than one diagnostic hypothesis or possibility as an explanation of the patient's symptoms and will refine this list as further information is obtained in the diagnostic process. A diagnosis is therefore fundamentally dependent on a personal interaction of a clinician with a patient, the sufficiency of communication between them, the accuracy of the patient's history and physical examination, and the cognitive energy necessary to synthesize a vast array of information" [14] Clinical reasoning involves thinking through various aspects of patient care to arrive at a reasonable decision regarding the prevention, diagnosis, or treatment of a clinical problem in a specific patient.[15]

The Two-Process Model of Clinical Reasoning comprises of

- Type 1 (Intuitive)
- Type 2 (Rational)

The intuitive approach is fast, more practical than logical, and depends on pattern recognition. Used mostly by experienced decision makers. Although it requires minimum effort, there is higher potential for error. The rational approach on the other hand is analytical and systematic. More often used by novice decision makers, it is time consuming as a lot of scientific rigor is involved to ensure an evidence-based decision. It is however more reliable with minimal error. Repetitive operation of Type 2 leads to Type 1 through recognition.[16] Well-crafted guidelines have contributed to improvement of diagnostic accuracy and promotion of effective therapy.

PRECISION MEDICINE

The medical community has long recognized the inherent uniqueness of patients as evidenced by the prevalence of specific disease entities within families and ethnicities, variable responses to medications, and diverse manifestations of a single pathology.[17] Nevertheless, medical treatment has maintained a broad approach to a heterogeneous population rather than a unique treatment approach to the individual patient.

Orthodox clinical medicine is premised on the ability to diagnose and manage patients based on a specific set of questions applied across all patient presentation scenarios to elucidate specific signs and symptoms. Although this system of medicine personalizes care to a patient, it is subjective, and similar signs and symptoms present in different patients may have varying underlying pathological mechanisms, and therefore require different management strategies. Advancements in laboratory medicine have helped augment clinical medicine by revealing underlying causative pathogens in diseases and refined medical diagnosis and treatment on a microscopic or histological level. However, recent technological advancements are leading medicine into a new era of disease prevention and treatment known as precision medicine.

Precision medicine is an approach that entails preventing or treating disease conditions based on specific genetic, biomarker, phenotypic expressions, and psychosocial characteristics of an individual with the goal of maximizing patient response and reducing adverse effects.[18] Precision medicine should not be confused with personalized medicine in that the former seeks to uncover and develop targeted therapies against similar genetic variants within a group of different individuals while the latter suggests the development of costly and unique therapies for each individual[19].

Precision medicine has been made feasible by advancements in technologies, which have provided extensive database of patient genetic data, characteristics, and powerful tools to analyze such data. Importantly, the cost of these technologies has decreased dramatically over time and enabled widespread utilization, and the developed tools have been used to research and develop treatments for rare genetic

diseases that were previously neglected by big pharmaceutical companies. Examples of such technologies include genetic sequencing, proteomics, metabolomics, bioinformatics, and computational biology[20,21]. These areas of research have drilled disease expression down to inter-individual variability in gene sequence, protein expression, and metabolism, and helped demonstrate how each of these may affect a patient's response to treatment.

The Barrack Obama administration in 2015 announced and supported a precision medicine initiative to stamp out cancer and diabetes[19, 20]. This initiative was borne out of the fact that drugs that are usually approved by the FDA are based on clinical trial results showing average patient response to tested experimental drugs, where only a fraction of the sampled patients actually respond to the treatment intervention and drive the interpretation of a successful or failed clinical trial[19]. As such, patients that are nonresponsive to the tested drugs do not benefit from the "successful" clinical trial. An extrapolation of the number of nonresponsive patients in clinical trials to the general population and a calculation of the potential number of nonresponsive patients to FDA-approved drugs in the larger population is alarming[19]. Thus, the need to stratify patients according to similar underlying genetic variants is imperative to improve outcome on a larger scale.

Although the precision medicine approach has been in existence in a loose sense in the context of organ transplantation, blood transfusion, and varying areas of medicine and disease conditions[18] (**Table 2**), scalability of this treatment approach did not mature until the accumulation of massive informative data, and revelation in the variability of expression of the same disease in different individuals4.

Euan A. Ashley provided a very lucid example of precision medicine in the treatment of cystic fibrosis as follows[19]: "An example of precision medicine is the treatment of cystic fibrosis with ivacaftor. Although genetic testing for the known cause of cystic fibrosis has existed for some time, there was no therapy directed at the underlying mutated chloride channel. In fact, the disease can be divided according to whether the defective channel reaches the cell surface or not. Ivacaftor increases the opening probability of the channel so that it is only effective in the subset

of patients in whom the channel reaches the surface. Such targeting of a drug to a precise subclass of patients is the hallmark of precision medicine. In fact, this particular drug development was further remarkable for the co-investment of the Cystic Fibrosis Foundation of $150 million in the development of the drug. That initial investment increased in value to $3.3 billion by the time of the sale of the royalty rights last year (2014)."

Table 2 - **Examples of Conditions in Which Precision Medicine Has Been Used.** (Adapted from J. Larry Jameson and Dan L. Longo, ***Precision Medicine – Personalized, Problematic, and Promising***. The New England Journal of Medicine, 2015.)[18]

Medical Field	Disease	Biomarker	Intervention
Cancer	Chronic myeloid leukemia	BCR-ABL	Imatinib[4]
	Lung cancer	EML4-ALK	Crizotinib[5]
Hematology	Thrombosis	Factor V Leiden	Avoid prothrombotic drugs[5]
Infectious disease	HIV/AIDS	CD4+ T cells, HIV viral load	Highly active antiretroviral therapy[6]
Cardiovascular disease	Coronary artery disease	*CYP2C19*	Clopidogrel[7]
Pulmonary disease	Cystic fibrosis	*G551D*	Ivacaftor[8]
Renal disease	Transplant rejection	Urinary gene signature	Antirejection drugs[9]
Hepatology	Hepatitis C	Hepatitis C viral load	Direct-acting antiviral agents[10]
Endocrine disease	Multiple endocrine neoplasia type 2	*RET*	Prophylactic thyroidectomy[11]
Metabolic disease	Hyperlipidemia	LDL cholesterol	Statins[12]
Neurology	Autoimmune encephalitis	CXCL13	Immunotherapy[13]
Psychiatry	Alcohol-use disorder	*GRIK1*	Topiramate[14]
Pharmacogenomics	Smoking cessation	*CYP2A6*	Varenicline[15]
Ophthalmology	Leber's congenital amaurosis	*RPE65*	Gene therapy[16]

* In the biomarker column, proteins or genes that are probed to find the specific variants of interest are shown. AIDS denotes acquired immunodeficiency syndrome, HIV human immunodeficiency virus, and LDL low-density lipoprotein.

Another illustrative example where precision medicine is of immediate importance and execution is cancer therapy. The reason for the drive towards precision medicine in cancer management is the avalanche of data yielded from heavy investment in research funding, drug development, and application of new technologies. This investment in cancer has produced enormous data that is still being analyzed in order to better understand the biology of cancer and its response to treatment. For example, through deep analysis of patient cancer data especially from The Cancer Genome Atlas (TCGA), it has been recognized that a group of different cancer types based on tissue or organ of origin utilize similar genetic pathways. Interestingly, similar cancer types also based on tissue or organ of origin in different individuals have been shown to utilize different genetic pathways [20]. Therefore, patients can be stratified along the line of similar genetic variants regardless of the cancer type rather than the tissue or organ of origin.

Of note, treatment of patients grouped on the basis of similar tissue or organ of origin has failed to yield results generalizable to larger populations. In this context, development and application of targeted treatments to patients involves a deeper understanding of individual cancer gene expression profiles as there are already tangible results to support the precision medicine approach. For instance, patients with lung cancer who have mutations in the epidermal growth factor receptor (EGFR) gene respond significantly better to tyrosine kinase inhibitors compared to those without such mutations[19, 22]. Also, in cases where cancers show resistance to targeted therapy, the precision medicine approach helps to uncover the genetic drivers of such resistance mechanisms downstream of the original mutation and could lead to the development of novel treatments to overcome such resistance.

Recent success in harnessing the immune system of a cancer patient to treat the patient's cancer is also limited by specific molecular and tissue limitations to immune cells that may differ from patient to patient. To this end, some approaches in treating cancer patients requires some form of precision medicine in which the immune cells from the cancer patient are extracted, and reprogrammed and expanded to very large numbers *in vitro* before being reinfused back into the patient.[20]

Apart from the disease setting, the genetic differences in healthy individuals that may predispose an individual to congenital defects, familial diseases, infections, or hereditary cancer may differ substantially. As such, a similar strategy that has been applied to cystic fibrosis and now cancer management can be exploited for the prediction and prevention of diseases before they even manifest in healthy persons. This management strategy will rely on thorough understanding of genetic expressions and changes in healthy populations.

To make precision medicine a reality in diverse disease scenarios, more genomic data (for example) is needed from very large cohorts of patients. This, in addition, to correlating gene data to patient medical records especially longitudinal phenotypic disease expressions over the natural history of a disease will help to establish a more holistic view of a healthy individual or patient and identify new opportunities to prevent or treat diseases in a precise manner[17].

For precision medicine to be successful, major stakeholders in different spheres of healthcare have to work towards a common goal in an organized health management ecosystem (**Figure 1 and Table 3**). [17, 23, 24] While orthodox clinical medicine is heavily dependent on extraction of relatively subjective data from a patient by a physician, and augmented by results from the laboratory diagnostic team, the precision medicine ecosystem is a little more complicated and aims to extract, align, and correlate an array of data from a large cohort of patients including the phenotypic data obtained by a physician or imaging, deeper analysis of patient specimen for routine tests and changes at the genetic level, longitudinal phenotypic changes of a patient based on electronic health records, and eventual analysis and interpretation of common underlying genetic features that could be used for patient stratification, prevention and treatment of diseases. The stakeholders involved in the precision medicine ecosystem include the patient, clinician, clinical laboratory scientists, basic and translational researchers, and bioinformatics specialists or computational biologists.

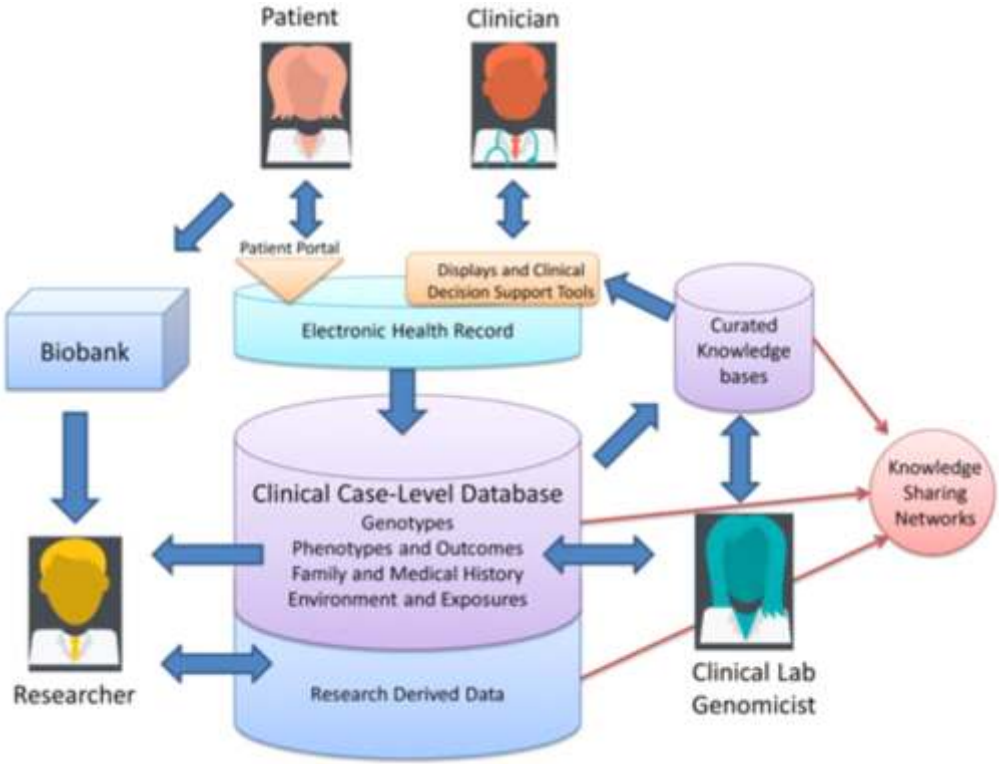


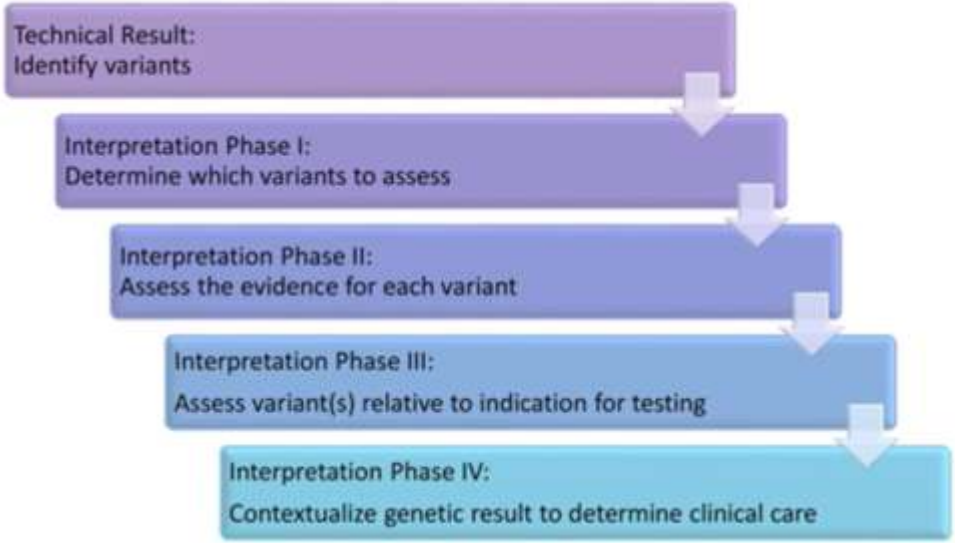
Figure 1| The precision medicine ecosystem. A key number of building blocks make up the precision-medicine ecosystem and connect major stakeholders to each other including patients, clinicians, researchers and clinical laboratories. Such building blocks include displays and clinical decision support tools augmented by curated knowledge that is supplied and shared among stakeholders. Case-level databases and biobanks receive case data and samples from clinical and research workflows. Researchers benefit from all of these information sources and also contribute to knowledge sources. Clinical laboratories leverage data and inform the clinical community as they assess genomic variation and its impact on human health. (Adapted with minor changes from Samuel J. Aronson and Heidi L. Rehm, ***Building the Foundation for Genomics in Precision Medicine***, Nature 2015)[17]

Table 3: Health Care Stakeholders and Their Roles in Ensuring the Success of Precision Medicine. Adapted from Reza Mirnezami et al., ***Preparing for Precision Medicine***, The New England Journal of Medicine, 2012.[24] ***Precision Medicine***, Nature 2015)[17]

Health Care Stakeholders and Their Roles in Ensuring the Success of Precision Medicine.	
Stakeholder	**Recommended Actions**
Government	Generation of transparent privacy laws Identification of socioeconomic priority areas likely to benefit most from precision-medicine strategies Public consultation regarding "opt in–opt out" strategies for research participation
Research industry	Development of effective clinical decision support tools for integration into electronic health records Setting up and conducting appropriate pilot studies for data collection in targeted precision-medicine areas
Biomedical community	Changes to undergraduate training to develop improved understanding of molecular mechanisms involved in disease Development and contribution to an evolving new system of disease classification incorporating emerging molecular information Introduction of a more transparent, participatory role for patients considered for recruitment to clinical trials
Pharmaceutical industry	Development of effective diagnostic tests with or without tandem therapeutic agents for management of conditions identified as major socioeconomic burdens
Patient groups	Increasing participation in health and well-being initiatives Use of novel means of providing data for research purposes, including social networks and mobile phone applications
Regulatory bodies	Ensuring that regulatory frameworks are in place to safeguard patient safety, while ensuring that scientific progress is not hampered

Once a precision ecosystem is developed, the key data that drives the interaction among stakeholders is the genetic data derived. Nonetheless, elucidation of disease phenotype by a physician cannot be eliminated during this process. In disease settings, identification of genetic variants will have to be parsed through several stages before the information obtained becomes meaningful for application in disease prevention or treatment (**Figure 2**).

Figure 2| Stages of the genetic interpretation process. Once genetic variants have been identified, they are filtered to select those of interest (step 1). Next, the evidence for each variant is assessed to determine the variant's clinical impact (step 2). One or more assessed variants are then interpreted with respect to the specific condition for which the patient is being investigated (step 3). Last, the overall genetic assessment is placed into the patient's clinical and personal context to inform the clinical-care decision-making process (step 4). (Adapted with minor changes from Samuel J. Aronson and Heidi L. Rehm, *Building the Foundation for Genomics in Precision Medicine*, Nature 2015)[17]



There are challenges to the successful implementation of precision medicine in diverse areas of medicine including cost of development and execution, unity of purpose among major stakeholders, obtaining consent from every patient seen by a physician to extract as much data as possible in order to build a large database, availability of advanced tools to analyze and interpret patient data in a rapid manner, and speed of determining a patient's underlying genetic data for therapeutic intervention following presentation and diagnosis, and the extent to which this approach can be leveraged for complex diseases and large populations.

PRECISION MEDICINE AND CONGENITAL CARDIOVASCULAR DISORDERS.

Clinical medicine and congenital heart defects

Congenital heart defect (CHD) refers to a defect in the structure of the heart and/or great vessels present at birth. It is the most common birth defect affecting 1% of live births[25] and the leading cause of infant mortality among birth defects. The cause of most CHD is largely unknown. Some CHDs have been linked to genetic disorders, maternal conditions, or environmental exposures, but the development of CHDs is likely a combination of genetic and nongenetic influences.[26] To assist in

identification of these maternal and environmental exposures, a thorough history taking is key.

Epidemiological studies have revealed that nearly 30 % of CHDs are associated with extracardiac anomalies.[27] These syndromic disorders are either caused by chromosomal anomalies or by point mutations, deletions, or insertions in key transcription factors or developmental genes. Physical examination for children with CHD must include a dysmorphology assessment to be able to make a syndrome diagnosis.

To diagnose CHD, important diagnostic tests often carried out include fetal echocardiography, pulse oximetry, echocardiography, chest x-ray, electrocardiography, cardiac catheterization and cardiovascular magnetic resonance imaging. Biomarkers such as troponin for myocardial damage, amino-terminal procollagen type III peptide (PIIIP) for myocardial ?brosis and stromal remodeling, and B-type natriuretic peptide (BNP)/N-terminal proBNP for cardiac load and heart failure have proven to be useful tools in ascertaining the condition of CHD in children. The biomarkers only help to evaluate pathological outcomes from specific hemodynamics, including volume and pressure overload, as well as cyanosis and pulmonary hypertension, associated with anatomical abnormalities.[28]

In investigating CHD, medical imaging is paramount. The application of echocardiography has revolutionized the imaging of CHD and marked the era of noninvasive imaging. Echocardiography has evolved from A-mode to M-mode echocardiography and progressed to encompass an array of related modalities including two-dimensional (2D), spectral and color Doppler, transesophageal, contrast, tissue Doppler, real-time three-dimensional (3D) transthoracic and transesophageal, speckle tracking, and handheld echocardiography.[29]

Echocardiography allows both the morphological and functional findings in CHD to be defined. It provides information on the heart position in the thorax, the atrial situs viscerum, the vein-atrial and the atrio-ventricular connections, the relationship between the ventricles, the ventriculo-arterial connection and the relationship of the great arteries (segmental analysis). In addition, the echocardiographic study enables a non-

invasive study of ventricular function in pediatric patients with CHD.[30] It has become the most efficient non-invasive imaging modality in diagnosis of CHD and the majority of children are referred for cardiac surgery based on echocardiography only. The diagnostic accuracy for describing cardiac morphology is extremely high. In a high volume academic pediatric cardiac centre, over a period of two and a half years, only 87 diagnostic error cases were identified in ≈ 50 660 echocardiograms performed.[31] Echocardiography is however limited by a small field of view, an acoustic window, and operator dependence.

Congenital heart defects in Nigeria

Ventricular septal defect (VSD) is the commonest CHD and Tetralogy of Fallot (TOF), the commonest cyanotic CHD reported in Nigeria (Table 4). We analysed the CHD distribution from 13 studies undertaken between year 1963 and year 2012 across Nigeria. [32]

Determinants of detection and accurate diagnosis of CHD include sophistication of the diagnostic methods used. Diagnostic methods used for CHD in Nigeria have evolved over the decades and may have influenced reports on the CHD types seen. In the 1960s–1980s, most cardiovascular evaluations were done by physical examination, ECG, chest X-ray, and selective angiography. By the 1990s, echocardiography had become available but, notably, diagnostic cardiac catheterization less frequently. In comparing the period before echocardiography became available in Nigeria (pre-echo) with the period thereafter, VSD remained the commonest CHD in Nigeria. In the pre-echo era, patent ductus arteriosus (PDA) was the next common type of CHD reported followed by pulmonary stenosis. This is in contrast to most studies in the echocardiography era where TOF or atrial septal defect (ASD) commonly followed VSD.

More recently, we published preliminary report of year 2014 data from a pediatric cardiac disease registry in Nigeria. Data from 17 centres showed a similar pattern of VSD being the commonest CHD followed by TOF.[33] When the prevalence in the Northern region of Nigeria was compared with the South, it showed that the prevalence of VSD was significantly higher in the North than in the South while the south had

higher prevalence of severe CHD. This was thought to be a reflection of poorer access to care in that region, with children having more severe lesions being more likely to die before presentation, given the older age at presentation in the North.

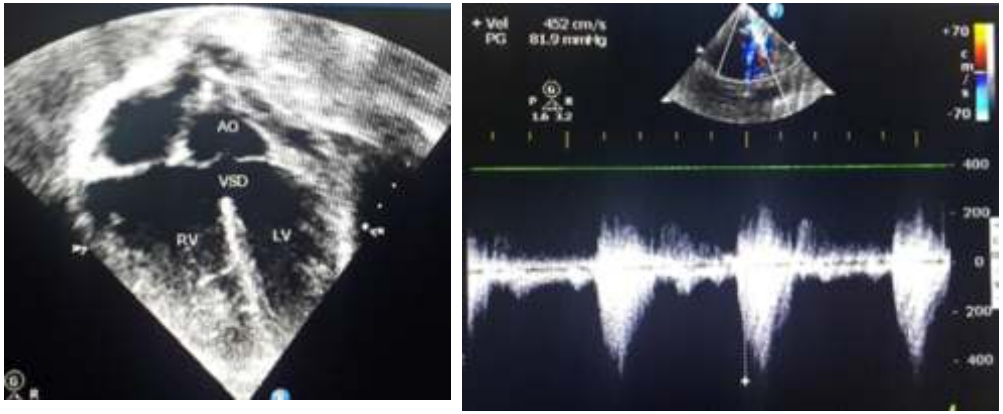
Clinical epidemiology of Congenital heart Defects in LUTH (2012-2017)

We undertook a study to evaluate CHD in Nigerian children based on both cardiac and extra cardiac phenotypes thus producing data useful for designing genetic, molecular and biomarker studies. Clinical and cardiac phenotypic data was obtained from 767 children with CHD seen in Lagos University Teaching Hospital, Nigeria between 2011 and 2017. From a total of 1010 potentially, eligible children who had an anomaly on echocardiography during the five-year study period, 243 children were excluded from further analysis due to having isolated PDA (155), isolated patent foramen ovale (PFO; 58), Aorto-pulmonary window (1), persistent left superior vena cava (1), cardiomyopathy without associated CHD (27) and CHD related to the vascular system such as vascular ring (1).

The frequency of CHD among 767 Children by Botto's Broad anatomical Classification[34] is shown in Table 4 with the majority of cases comprising of septal defects (43%). Other commonly seen defects were conotruncal (Figures 3a and 3b), atrioventricular and right ventricular outflow tract obstruction lesions. There were 215 (28%) cases with extra cardiac malformations among the 767 children with CHD. Out of these 215 cases, the particular syndromes were clinically identified in 119 (15.5% of total) cases. The top three identified syndromes were Down syndrome, congenital rubella syndrome and Marfan syndrome. The commonest CHD in Down syndrome was atrio ventricular septal defect (AVSD; 60.4%). Pulmonary stenosis with PDA was commonly seen in congenital rubella syndrome while cases of Marfan syndrome had aortic root dilatation with mitral valve prolapse. Figure 4 shows contribution of syndromes to CHD by broad groups.

Table 4 - Frequency of CHD among 767 Children by Botto's Broad Anatomical Classification.[33]

Broad groups of CHD	Frequency	Percentage
Septal defects	330	43.0
Conotruncal defects	182	23.7
Atrioventricular septal defects	75	9.8
Right ventricular outflow tract obstruction (RVOTO) lesions	56	7.3
Septal +RVOTO	39	5.1
Left ventricular outflow tract obstruction (LVOTO) lesions	16	2.1
Singleventricle/complex	12	1.6
Heterotaxy	11	1.4
Anomalous pulmonary venous return	8	1.0
Mitral valve malformation	8	1.0
Cortriatriatum	5	0.7
Septal +LVOTO	4	0.5
Others	21	2.7
TOTAL	767	100



Fig, 3a- 2D Echocardiography image of a 15 year old with TOF, a conotruncal lesion showing a malaligned VSD, overiding aorta and right ventricular

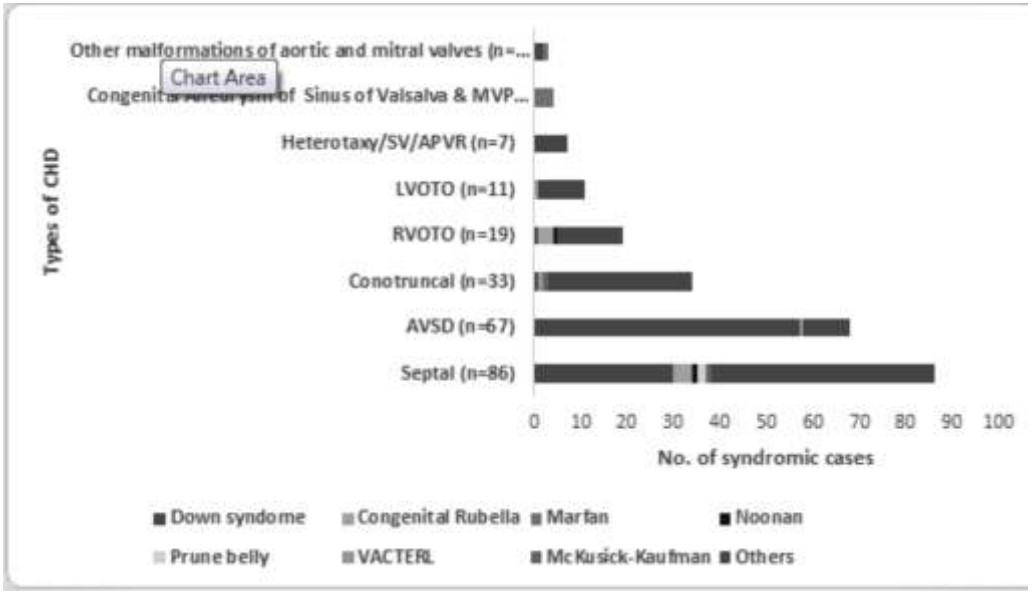


Fig. 4 - Contribution of syndromes to CHD by broad groups[33]

Molecular diagnosis and genomics in CHD

In clinical management of a patient with CHD, knowing the genetic pattern of that defect provides answers to relevant questions such as - is another important organ system involved? what is the prognosis for clinical outcome? what is the probability that another child with this disease will be born to this family? do other members of the family need to have genetic tests done? Technological advances in diagnosis and management have resulted in more of patients with CHD surviving to adulthood. It is currently estimated that there are more adults living with CHDs than children.[35] The importance of understanding the underlying genetic pattern becomes even more relevant as individuals with CHD survive into adulthood and start having children of their own.

CHD has been observed to be extremely heterogenic with identical pathogenic CHD mutations causing a variety of distinct malformations. Genetic contributors to CHD include disorders of chromosome copy number (e.g., Down syndrome), sub chromosomal deletions (e.g., 22q11.2del) and duplications (chromosome 1p21dup), rare monogenic pathogenic variants, rare oligogenic deleterious variants, and common variants.[36, 37.]

Genetic tests refer to analysis of human chromosomes, DNA, RNA, Proteins, or metabolites in order to detect alterations related to a heritable disorder. Molecular diagnostic genetic/genomic techniques have evolved from search for abnormal number of chromosomes and mutations that lead to rare inherited disorders to tests that analyse multiple genes. The most common clinical genetic tests utilized in CHD are karyotypes, chromosomal microarray, targeted FISH (Fluorescence in-situ hybridization), directed panel sequencing, whole-exome sequencing, and whole genome sequencing.[36] Despite the advances in genomics, more than 50% of genetic aetiology of CHD remains unknown. Noncoding genetic, epigenetic, and environmental factors, among others are suggested possible explanations for the unidentified causes. Figure 5 shows an outline of how to proceed in genetic testing for patients with CHD.

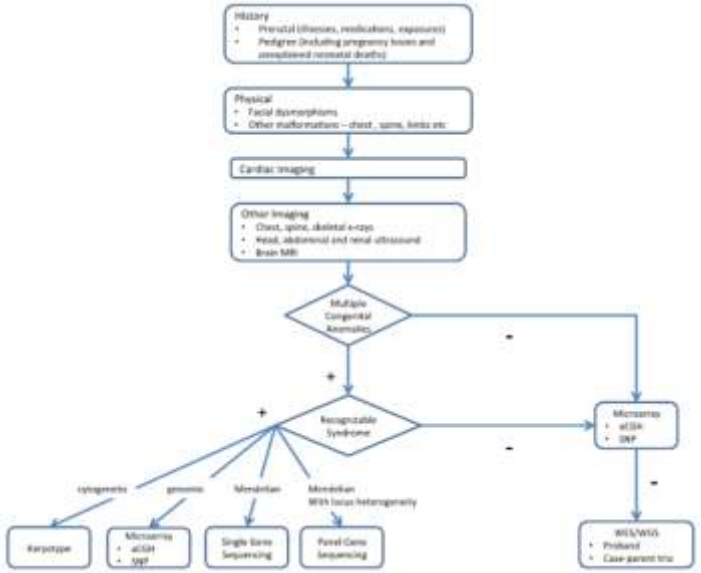


Fig. 5 - The Genetic Workup for Congenital Structural Heart Disease: From Clinical to Genetic Evaluation

(Kruszka P, Sable CA, Belmont JW, Muenke M. 2015. The Genetic Workup for Congenital Structural Heart Disease: From Clinical to Genetic Evaluation. In: Muenke, M., Kruszka, P., Sable, C., Belmont, J. (eds.): Congenital Cardiovascular Anomalies: Molecular Genetics, Principles of Diagnosis and Treatment. Karger Publishing, Basel, Switzerland, p238-254).

Aneuploidy: CHD associated with cytogenetic abnormalities account for 9-18% of genetic causes of CHD. The commonest aneuploidy is Trisomy 21 where 40-50% of affected patients have CHD[37] especially Atrioventricular septal defect.[33] The genetic architecture of the CHD in patients with Down syndrome is suggested to be through DSCAM and COL6A.[38] Other aneuploidies are Trisomy 13 and 18; and Turner syndrome (monosomy X).

Copy number variation: These are genetic structural alterations where large sections of DNA from 1kb to several megabases are either deleted

or duplicated resulting in altered changes in the dosage of genes in the neighbourhood of the CNV. CNVs are either de novo or inherited. 22q11.2 deletion syndrome is the commonest human microdeletion and is associated with CHD in nearly 75% of cases. Other known CHD-associated CNVs include del 8p23, del 7q11(William syndrome) and del 11q24-25 (Jacobsen syndrome).[36] Conotruncal defects such as TOF, interrupted aortic arch or truncus arteriosus are commonly seen in patients with CNVs.[37]

Single gene syndromes

RASopathies: These are a group of autosomal dominant disorders with overlapping cardiac, growth, facial, and Neurodevelopmental features caused by genes involved in the RAS mitogen-activated protein kinase pathway. The spectrum of RASopathies includes Noonan syndrome (NS), cardiofaciocutaneous syndrome, Costello syndrome, and NS with multiple lentigines. Heterozygous *PTPN11* missense pathologic variants explains 50% of Noonan syndrome cases.[39] An additional 30% can be explained by mutations in one of the RAS MAP kinase pathway genes including *SOS1, RAF1, RIT1, KRAS, SHOC2, NRAS, SOS2, BRAF, A2ML1, LZTR1, MYST4, RASA2, RRAS, SPRY1*, and *SYNGAP1*.[40]

Ciliopathies: These are genetic disease characterized by dysfunction of the cilia structures and function. Ciliopathies are associated with some syndromes such as heterotaxy, Bardet-Biedl Alstrom, McKusick-Kaufman, and Ellis van Creveld syndrome. In those with Heterotaxy syndrome, unbalanced atrio-ventricular septal defect is seen in 50-95% of cases. [37]

Chromatin modifiers: This involves cardiac transcription factor mutations, such as those involving TBX5 (associated with Holt-Oram syndrome) and TBX1 (associated with some features of 22q11.2 deletion syndrome), have major extracardiac manifestations. Others are mutations of the chromatin modifiers, *KMT2D* and *KDM6A*, which encode for lysine (K)-specific methyltransferase 2D and lysine-specific demethylase 6A, causing Kabuki syndrome, a developmental disorder affecting the heart, brain, urogenital system, craniofacial structures, and linear growth (height). Heart defects, which can range from mild (atrial septal defect, ventricular septal defect, patent ductus arteriosus, coarctation of the aorta) to more severe (TOF, single-ventricle CHD), occur in 31% to 58%

of Kabuki syndrome patients.[41, 42]

Damaging mutations in the chromatin modifier genes have been found to have the highest risk of conferring a neurodevelopmental (ND) abnormality phenotype.

Single gene (non-syndrome)

De novo variants

Earlier genes implicated in inherited CHD belong to a group of cardiac transcription factors that includes *NKX2.5*, the GATA family of zinc-finger proteins, T-box factors including TBX5 and TBX1 and MEF2 factors. In recent times, exome sequencing analysis has demonstrated that ~10% of CHD can be explained by de novo single-nucleotide variants. Exome sequencing of 1,213 CHD parent-offspring trios identified an excess of protein-damaging *de novo* mutations, especially in genes highly expressed in developing heart and brain. [43]

Structural proteins: While more commonly associated with cardiomyopathy, mutations in genes encoding for components of the cardiac sarcomere have been determined to be responsible for familial and sporadic CHD. Examples include mutations in *MYH7* (b myosin heavy chain) in individuals with Ebstein anomaly of the tricuspid valve, in *ACTC1* (cardiac a actin) in familial ASD, and in *MYH6* (a myosin heavy chain 6) in autosomal dominant familial ASD and sporadic cases of more complex CHD, including Shone complex and Hypoplastic left heart syndrome.[37,44]

CONGENITAL HEART DEFECT GENOMICS IN NIGERIA

There are few available genetic studies undertaken in Africa have that focused on CHD.[45-48] African populations have the greatest genetic diversity of any continental population group and offer the prospects of finding novel mutations that could advance our knowledge of the disease. To the best of our knowledge there has been no Genome Wide Association Study (GWAS), Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) study of CHD in a Nigerian population. In the premise of this, a collaborative research work with researchers in NIH (*Protocol T-HG-0098: "The Genetic Basis of Congenital Heart Disease in Africa")* was started in 2014 under the leadership of Maximilian Muenke MD with the following specific aims:

- To determine, identify, and estimate the prevalence of novel and known CHD causing mutations in African populations
- To investigate phenotype and genotype correlations in patients with CHD
- To better understand the genetics of CHD by employing emerging genomic technologies combined with functional studies.

All known aneuploidy syndromes were excluded. This has involved enrolling CHD trios (proband and their parents) presenting at the Lagos University Teaching Hospital(LUTH) in Nigeria. This collaboration has facilitated the development of a strong infrastructure of enrollment of families with CHD that has enabled over 300 Nigerian children with CHD (along with their parents) to be enrolled. Clinical enrolment, including echocardiography, and blood sample collection is done on site in Lagos, Nigeria. Blood samples are stored at -70^{0}C in Central Research Laboratory of College of Medicine, University of Lagos and shipped periodically to National Institutes of Health (NIH). Illumina OmniExpress array is used to profile structural variants and whole exome sequencing and capture (WES) are done at the NHGRI, NIH labs of the US collaborators (Figure 6).

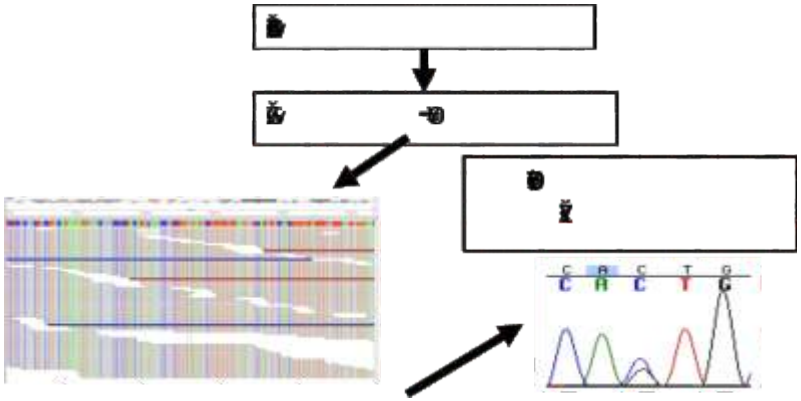


Fig. 6 – Illustrates the genetic analysis pipeline for the study.

The pipeline has been completed for 110 probands (55.5% male). The overall distribution of preliminary findings for the Nigerian samples in the collaboration (total n=110) are shown in Figure 7.

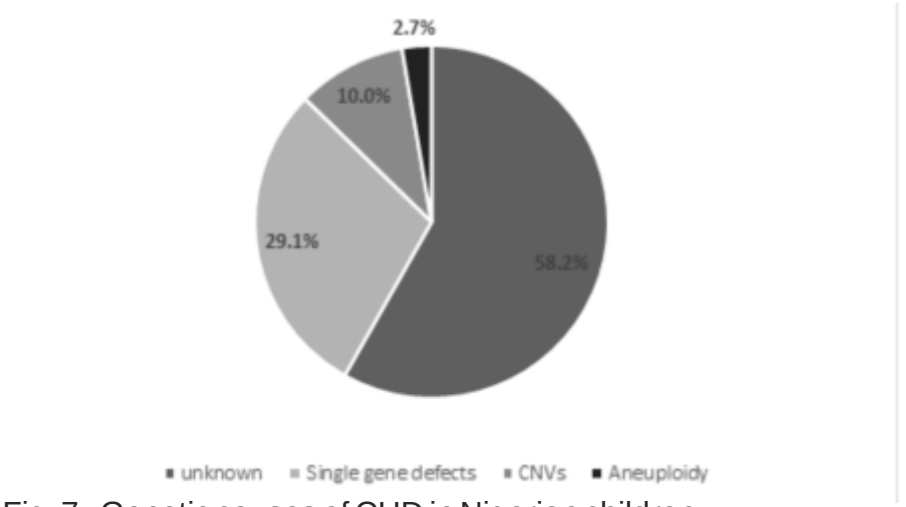


Fig. 7 - Genetic causes of CHD in Nigerian children

The total yield of causative genetic determinant was 41.8%. Thirty-two patients (29.1%) had pathogenic mutations in genes known to cause CHD either in humans or mouse models. Included among the isolated pathogenic mutation genes are *JAG1, CHD7, MAP2K1, CLCN1* and *SLC26A8* (Table 5). Inheritance data was available for 18 of the 32 cases with single dene defects and only 3 cases had inherited the gene from their parents (two from father and one from mother). All others were de novo variants.

Structural or copy number variations were present in 10% (n=11) with the most common condition being 22q11.2 deletion syndrome. Others observed include 1q duplication, 8p23.1 deletion (GATA4), 16p11.2 duplication and 15q13.3 deletion syndrome. The three patients with abnormal chromosomal copy number (aneuploidy) had Trisomy 13, 18 and XXX syndromes. Known syndromic cases such as Down syndrome had been excluded.

Table 5 – Selected pathogenic mutant genes in CHD in Nigeria

ID	Inheritance	Variant	Comment	Phenotype	Gene	Pathogenicity criteria
12552	de novo	p.D67N	Cardio-facio-cutaneous syndrome	ASD, PS	*MAP2K1*	ClinVar; ACMG 2015
11764	de novo	p.V184D	Tuberous Sclerosis	Ventricular mass	*TSC2*	ACMG 2015
12779		JAG1 del XHMM	Alagille syndrome	PS	*JAG1*	HGMD
11759	de novo	p.R483X	No associated OMIM syndrome	SV, IAA	*XPOT*	Intervar
12419	de novo	p.L394X	No associated OMIM syndrome	TOF	*PRKCB*	Intervar
12749	de novo	p.W1456X	Emery-Dreifuss muscular dystrophy 5, autosomal dominant	TA	*SYNE2*	Intervar
12728	Inh_het_father	p.R588X	Myotonia congenita, (dominant or recessive)	ASD, VSD, PDA	*CLCN1*	ClinVar
12160	de novo	p.S235F		VSD, Non-compaction cardiomyopathy	*ACTC1*	ACMG 2015
12480	de novo	p.E394K	Spermatogenic failure (Dirami et al. 2013)	BAV, COA.	*SLC26A8*	ClinVar

ASD- Atrial septal defect; PS- Pulmonary stenosis; SV- Single ventricle; IAA- Interrupted aortic arch; TOF -Tetralogy of Fallot; TA- Tricuspid atresia; VSD- Ventricular septal defect; PDA- patent ductus arteriosus; BAV- Bicuspid aortic valve; COA- coarctation of the aorta; HGMD- Human Gene Mutation Database; ACMG- American College of Medical Genetics and Genomics.

PRECISION MEDICINE AND CONGENITAL HEART DEFECTS

The impact of genetic diagnosis of CHD on clinical outcomes

Clinical outcome measures that can be affected in patients with CHD include neurodevelopment, growth, ventricular function, and survival. Table 6 shows the impact of major categories of genetic determinants of CHD and their effect on selected clinical outcomes.

In Down syndrome, repair associated mortality risk is not higher when compared with other patients with CHD except for single-ventricle palliation, a risk they share with patients who have Turners syndrome. There is however increased morbidity including longer postoperative hospital stay, increased risk of respiratory and infectious complications, pulmonary hypertension, chylothorax and postoperative complete heart block in patients with Down syndrome.

For patients with 22q11.2 deletion surgical outcome is poorer for certain types of CHD, including pulmonary atresia with ventricular septal defect and interrupted aortic arch. Surgical repair of tetralogy of Fallot in them typically requires longer cardiopulmonary bypass times, longer postoperative intensive care unit stay and worse quality of life on long-term follow-up. Most importantly, because of associated immune deficiency in 22q11.2 deletion syndrome, special handling of blood products is often required during the operation and perioperative setting. To avoid severe complications such as graft-versus-host disease and overwhelming cytomegalovirus infection it is advised that only CMV seronegative/irradiated blood products be administered to patients with 22q11.2 deletion syndrome.

Williams-Beuren syndrome (WBS) is another syndrome with copy number variations (CNV) as the genetic architecture of its associated CHD. Clinically observed outcomes in these patients include growth deficiency, cognitive and behavioral deficits. In addition, those with biventricular outflow tract obstruction and/or coronary ostial stenosis, are at risk for sudden death, especially when undergoing perioperative or periprocedural sedation, requiring careful anesthetic management and monitoring.

Noonan syndrome (NS) patients commonly have valvar pulmonary stenosis. Severe cases need intervention which can be by balloon valvuloplasty or surgery. NS patients with pulmonary stenosis are often not considered to be good candidates for balloon valvuloplasty due to the high rates of required reintervention (65%) after this procedure. As shown in these instances, the knowledge of genetic determinants of patients with CHD can enable clinicians adjust therapy or patient management strategies for more precise treatment. As more data on CHD outcomes in relation with underlying genetic determinants become available, stratifying subjects by genetic risk for specific outcomes to identify different subpopulations responsive or resistant to the treatment or intervention will be a possibility.[37]

Challenges of Genomics

As the field of genomics continues to advance technologically, major analytical and interpretative challenges emerge. These range from the validation of large numbers of genomic changes in a patient, to the economic feasibility of this approach and its deployment in standard care, to managing the terabytes of data that accompany a single sequenced genome.[49, 50]

Table 6- Impact of major categories of genetic determinants of CHD and their effect on selected clinical outcomes.[37]

Type of Genetic Variation	Outcome Domain				
	Survival	ND	Growth	V Function	Notes
Chromosomal abnormality					
Down syndrome	+/- [a]	++	+++	-	Higher mortality for single V heart defects; other defects unaffected[a]
Trisomy 18	++	++++	++++	-	
Trisomy 13	+++	++++	++++	-	
Turner syndrome	-	-	+++	-	
CNV					
22q11.2	+/- [a]	+	++	-	Higher mortality for pulmonary atresia with VSD; other defects unaffected[a]
Williams syndrome	+	+	++	-	
1p36 del	+	+	+	-	
Others	+	+	+	-	
Single gene disorders (rare variant)					
RASopathies	+/- [a]	- to ++	+	-	Higher mortality in cases with severe, early HCM[a]
Ciliary defects	-	-	-	-	Increased respiratory complications
Transcription factor	-	-	-	-	
Chromatin remodeling	-	+	+	-	
Sarcomeric	-	-	-	++	
Single gene disorders (common variant)					
ApoE (e2 allele)	-	+	-	-	
RAAS pathway	-	-	-	+[a]	Effect on ventricular remodeling in single V heart disease*
VEGFA variant	+	-	-	+	
Adrenergic signal	+	-	-	-	

As an example, I describe a clinical case under my care. When a young child developed a respiratory illness at 4 months of age and was taken to a nearby secondary health facility, he was referred to LUTH on account of heart murmur. Clinical evaluation and echocardiography diagnosis revealed a Tetralogy of Fallot. Successful Medical and surgical treatment followed.

At the age of 6 years, the following clinical features were observed: poor concentration, slow learning and yet to read. Other observations included aggressive behavior towards younger siblings, poor social skills and poor school performance. In view of his clinical diagnosis and cardiac surgery, these observations were categorized as complications of the

CHD/intervention. However, following enrollment into our genetic study, the genetic diagnosis of 22q 11.2 deletion was made by chromosomal microarray.

Features of 22q 11.2 deletion syndrome include: cardiac abnormality (commonly interrupted aortic arch, truncus arteriosus and tetralogy of Fallot), abnormal facies, thymic aplasia, cleft palate and hypocalcemia/hypoparathyroidism. Others are thrombocytopenia, significant feeding difficulties, gastrointestinal problems, and hearing loss. Skeletal differences - mild short stature, abnormalities of the spinal bones. developmental delays (delayed growth and speech development), as well as learning disabilities could occur. Attention deficit hyperactivity disorder (ADHD) and developmental conditions such as autism spectrum disorders that affect communication and social interaction. Clinical features seen later in life include mental illnesses such as schizophrenia, depression, anxiety, and bipolar disorder. The genetic diagnosis gives a more precise diagnosis that accounts for all the features presented clinically but also provides a better idea of the long-term prognosis.

The patient is currently being co-managed with the child psychiatrist.

DIGITAL FACIAL ANALYSIS TECHNOLOGY

This is an automated non-invasive technology based on quantitative imaging and machine learning (a form of artificial intelligence). The fact that symptoms of some genetic syndromes such as Down syndrome present as facial morphology (or geometry) and appearance (or texture) patterns, has paved the way for developing a computer-aided diagnosis system for syndromic genetic diseases based on photogrammetry.
Geometric and texture features are extracted based on the automatically located facial landmarks, followed by feature combination and selection. Some of the geometric features include orientation of the right eye, length of upper part of nose, length of right palpebral fissure, length of lower nose, thickness of upper lip, orientation of left eye, length of philtrum, distance between inner corners of eyes and angle of left corner of right eye (Figure 8).

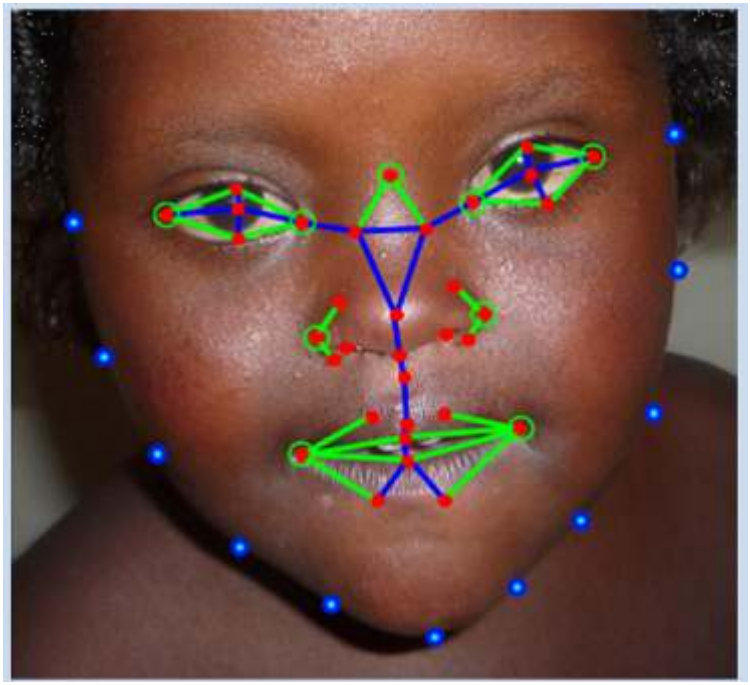


Fig. 8 - Facial landmarks on a down syndrome patient of African descent.[51]

After feature extraction and selection, the syndrome can be identified from a non-syndrome group by using four individual classifiers separately, including SVM with radial basis function kernel (SVM-RBF), SVM with linear kernel (SVM-linear), RF and Linear discriminant Analysis (LDA). A classifier is a machine learning algorithm or mathematical function. The concept of facial recognition for diagnosing genetic syndromes is not new but mostly practiced by doctors and specialists. Doctors skilled enough to make such diagnosis from facial recognition are insufficient. Therefore, a technology that aids diagnosis of genetic syndromes brings expertise to areas where specialized genetic expertise is lacking. This technology can be used in the newborn period without the need for blood tests or specialized clinics.

APPLICATION OF DIGITAL FACIAL ANALYSIS TECHNOLOGY IN SYNDROMIC CHD

While experienced clinicians often can recognize certain clinical syndromes from their facial features, this process is subjective, prone to error and may miss subtle features. In addition, human malformation syndromes often appear different in different parts of the world and even experienced clinicians can have trouble identifying genetic syndromes in young children, particularly from different ethnic backgrounds. Digital facial technology can help make a more precise diagnosis.

Down syndrome: This is the commonest aneuploidy in live births and a common cause of CHD. In a study that involved 13 countries and four ethnic groups, we applied the digital facial analysis technology to the DS population. [52] On physical examination only, the most common features, and the only two findings found in over half of participants were upslanting palpebral fissures and flat facial profile with minimum prevalence's of 61% and 51%, respectively. There was large variation in facial findings between all studies, even within the same ethnic groups. Using a more objective approach with digital facial recognition technology in patients and controls who are Caucasians, Africans or African American, and Asians, the Asian group had the least number of significant geometric features at four compared to Caucasians at eight and Africans at seven.

Caucasians and Africans shared the most significant anatomical features at six geometric measures including the upslanting of the palpebral fissures, the length of the nose and the distance between the medial canthi. Interestingly, the upslanting of the palpebral fissures was not a discriminative feature of DS in the Asian group. Sensitivity, specificity, and diagnostic accuracy were 0.853, 0.856, and 0.854, respectively for a combined analysis of the entire cohort using only geometric features. When using both geometric and texture measures, sensitivity increased to 0.961, specificity to 0.924, and accuracy to 0.943 ($P<0.001$). Sensitivity, specificity, and accuracy improved when combining geometric and texture features for distinct groups ($P<0.001$).[51]

The study was thus able to demonstrate the accuracy and promise of digital facial analysis technology in the diagnosis of Down syndrome internationally.

22q11 deletion syndrome: In a similar study on a population of 22q11 deletion syndrome cases, we found that the phenotype of 22q11.2 DS varied across population groups. Only two findings, congenital heart disease and learning problems, were found in greater than 50% of participants. When comparing the clinical features of 22q11.2 DS in each population, the proportion of individuals within each clinical category was statistically different except for learning problems and ear anomalies ($P < 0.05$). However, when Africans were removed from analysis, six additional clinical features were found to be independent of ethnicity ($P \geq 0.05$)-learning problems, developmental delay, palatal abnormalities, narrow palpebral fissures, nose anomalies, hooded eyelids, psychiatric illness, and ear anomalies.

Using facial analysis technology, we compared 156 Caucasians, Africans, Asians, and Latin American individuals with 22q11.2DS with 156 age and gender matched controls and found that sensitivity and specificity were greater than 96% for all populations. This confirmed that Digital Facial analysis technology can assist clinicians in making accurate 22q11.2 DS diagnoses.[52] (Figure 9).

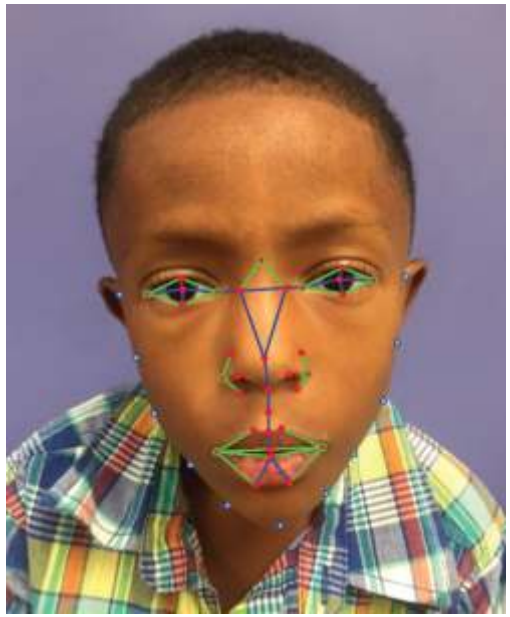


Fig. 9 – Facial landmarks on a 22q11.2 deletion syndrome patient of African descent.[52]

Noonan syndrome: Individuals from 20 countries of diverse populations with Noonan syndrome were also evaluated clinically and by digital facial analysis technology. Clinical data and images from 125 individuals with NS were studied. Across the African, Asian, Latin American groups, NS was phenotypically similar with only 2 of 21 clinical elements showing a statistically significant difference. The most common clinical characteristics found in all population groups included widely spaced eyes and low set ears in 80% or greater of participants, short stature in more than 70%, and pulmonary stenosis in roughly half of study individuals. Using facial analysis technology, we compared 161 Caucasian, African, Asian, and Latin American individuals with NS with 161 gender and age matched controls and found that sensitivity was equal to or greater than 94% for all groups, and specificity was equal to or greater than 90%.[53] (Figure 10).

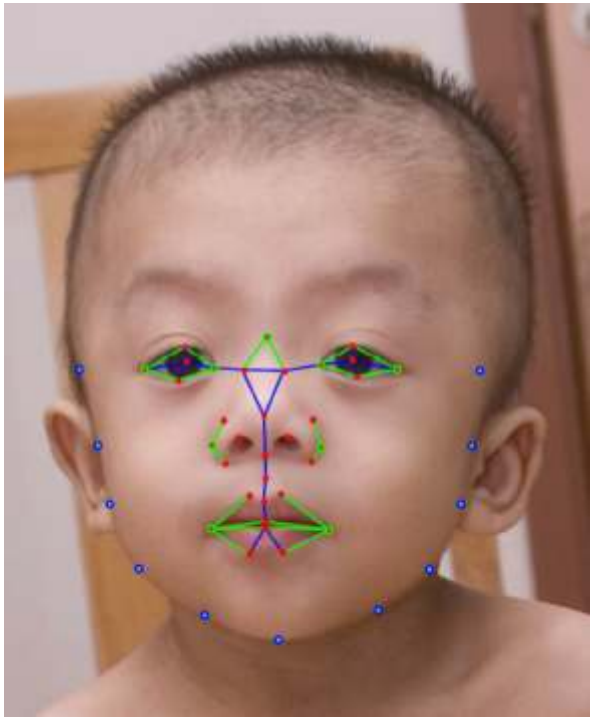


Fig. 10- Facial landmarks on a Noonan syndrome patient of Asian descent.[53]

By using photography and image analysis, this automated assessment tool has the potential to improve the diagnosis rate and allow for remote, non-invasive diagnostic evaluation for dysmorphologies in a timely manner.

Face2gene, available free online is a deep phenotyping app that facilitates comprehensive and precise genetic evaluations using the digital facial analysis technology. The steps are easy. You take a picture of the patient and upload it to Face2Gene via an APP you had downloaded on your smart phone or laptop. Enter anthropometric measurements and/or add case data. Face2Gene compares pictures of a patient's face with those of disease composites and provides you with a series of syndrome suggestions, from highest risk to the lowest risk.

Today a child in a Nigerian clinic is being diagnosed with Tetralogy of Fallot. The parents will be told that he/she needs cardiac surgery. They will be told that the prognosis after surgery is very good and the child can live a normal life thereafter. Years down the line, patient cannot meet the educational expectation of parents and becomes a psychiatric case. What happened? Despite our excellent clinical skills applied on patients, our comprehension of the big picture of our patients is limited. Sadly, we give prognosis based on that limited knowledge.

Now consider a Nigeria where the scenario is different. Molecular research has revealed a series of molecular factors that underlie CHD. Looking at the patient's medical history, phenotype delineation by clinical examination and cardiac imaging; and genome information along with other molecular data, the doctor is able to identify precisely what the patient is suffering from and all potential short term and long-term events. This empowers the clinician to devise a customized treatment plan including needed consults. A large data set allows the patients to be subcategorized appropriately and given precise management in groups. Prognostic information becomes more realistic.

TOWARDS PRECISION MEDICINE IN NIGERIA

Precision medicine requires diagnostic facilities as well as trained personnel. However, a critical prerequisite is the evidence base. For

precision medicine to become a reality we need more research and more data that is applicable to indigenous populations. This is an issue in Nigeria given the modest investment in medical research of local relevance.

The Human Heredity and Health in Africa (H3Africa) Project. Jointly funded by the National Institutes of Health (NIH) and the Wellcome Trust, H3Africa has invested in several major grants to African investigators for genomics research, capacity building, and improving infrastructure for genome research in Africa (H3Africa Consortium, 2014). Nigerian sites are participating in several of these projects, including studies of stroke, chronic kidney disease, febrile illness, cervical cancer, glaucoma, and ELSI (bioethics) among others. Several H3Africa bioinformatics nodes are also in Nigeria.

These projects are currently contributing to the development of genomics/genetics facilities (genotyping, sequencing, bioinformatics), building manpower and studying these disorders for the first time in Nigeria.

There are also other ongoing genetics studies between Nigerian researchers and international collaborators such as studies on cleft lip/palate and motion disorders. The ongoing studies should improve the evidence base on which to build precision medicine initiatives in Nigeria. National policies and programs can then combine the infrastructure, manpower and evidence base to improve health care.
To ensure continuity and growth of the budding activities geared towards precision medicine in Nigeria, a low hanging fruit is structuring medical undergraduate training to develop improved understanding of molecular mechanism of disease conditions.

For CHD, do we currently know all the genetic determinants of CHD? The answer is No. closing the gap in knowledge in the genetic determinants of CHD is fundamental to precision child Health cardiovascular medicine.
Key elements necessary to advance the field of precision medicine in congenital cardiovascular disorders are

- Proper delineation of the phenotypic spectrum of CHDs;
  - Newborn screening for early diagnosis of critical CHD
  - Improved clinical diagnostic skill for all CHD
  - Careful inspection and documentation of all dysmorphic features
  - Accurate echocardiography delineation of CHD
  - Establishment of National CHD Clinical Data Registry
- Defining the molecular genotype/phenotype
- Availability of more genomic tests locally
  - Harnessing local resources
  - Identifying needed resources that are not yet available and how to make them accessible/locally available
- Mindset for development of precision medicine: The political will to enhance infrastructure for precision medicine in Nigeria is needed by policy makers. In addition, we the clinicians/researchers have to develop that mindset to be able to advocate for a new way of dealing with disease.

Future efforts in precision medicine should not aim only to correct or to palliate but also toprevent disease progression and comorbidities.

CONCLUSION

Precision medicine is not a substitute for clinical medicine. It simply makes it more precise. I have used the example of congenital heart defects to illustrate how we can use two modern technologies: molecular genetic diagnosis and digital facial recognition technology to provide precision medicine for patients and their families. The clinical diagnosis provides an important starting point but other tests refine the diagnosis and consequently, treatment options and prognosis. In other words, a more precise diagnosis guides treatment decisions for best outcome and provides information for accurate prognosis.

In our respective clinical practices, we can continue to facilitate better precision medicine by continuously building the evidence base through research, providing training and creating better infrastructure.

Thank you.

ACKNOWLEDGEMENT

I am hugely indebted to Almighty God for his marvelous help to me. I also wish to appreciate the following people who He used to make this lecture possible.

- My family.
- Dr Maximilian Muenke (NIH)
- Dr Adebowale Adeyemo (NIH)
- Dr Paul Kruszka (NIH)
- Prof Christy Okoromah
- Dr Felix Nwajei
- Sue Dziedzic
- Dr Ogochukwu Sokunbi
- Dr Nnenna Kalu
- Dr Akinsanya Olusegun-Joseph
- Mr. Desmond Ikebudu
- Mr. David Bala
- Miss Helen Chinaka
- Mr. Friday Edim
- Dr. Emeka Ugwu
- Dr Christopher Esezobor
- Late Dr Ekopimo Ibia.
- The Professor and Head, Department of Paediatrics, CMU- Prof Edamisan Temiye.
- The Dean, Faculty of Clinical Sciences, College of Medicine, University of Lagos. Prof. J.D. Adeyemi
- The Provost , College of Medicine, University of Lagos – Prof. FEA Lesi.
- The current Deputy Vice Chancellor (Development Services) Prof. Folashade Ogunsola
- All Residents and interns who rotated through the Paediatric cardiology unit of Lagos University Teaching Hospital especially from 2014 till date.
- All past and current staff of the Cardiovascular lab, Lagos University Teaching Hospital
- Last but not the least all the children with CHD who have been my teachers and provided the data shared today.

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