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Evaluation of Knowledge Regarding Diagnostic Strategies for Genetic Diseases in Select Residents

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EVALUATION OF KNOWLEDGE REGARDING DIAGNOSTIC STRATEGIES FOR GENETIC DISEASES IN SELECT RESIDENTS

A

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“Evaluation of Knowledge Regarding Diagnostic Strategies for Genetic Diseases in Select Residents”

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Genetics education for physicians has been a popular publication topic in the United States and in Europe for over 20 years. Decreasing numbers of medical genetics professionals and an increasing volume of genetic information has created a dire need for increased genetics training in medical school and in clinical practice. This study aimed to assess how well pediatrics-focused primary care physicians apply their general genetics knowledge to clinical genetic testing using scenario-based questions. We chose to specifically focus on knowledge of the diagnostic applicability of Chromosomal Microarray (CMA) technology in pediatrics because of its recent recommendation by the International Standard Cytogenomic Array (ISCA) Consortium as a first-tier genetic test for individuals with developmental disabilities and/or congenital anomalies. Proficiency in ordering baseline genetic testing was evaluated for eighty-one respondents from four pediatrics-focused residencies (categorical pediatrics, pediatric neurology, internal medicine/pediatrics, and family practice) at two large residency programs in Houston, Texas. Similar to other studies, we found an overall deficit of genetic testing knowledge, especially among family practice residents. Interestingly, residents who elected to complete a genetics rotation in medical school scored significantly better than expected, as well as better than residents who did not elect to complete a genetics rotation. We suspect that the insufficient knowledge among physicians regarding a baseline genetics work-up is leading to redundant (i.e. concurrent karyotype and CMA) and incorrect (i.e. ordering CMA to detect achondroplasia) genetic testing and is contributing to rising health care costs in the United States. Our results provide specific teaching points upon which medical schools can focus education about clinical genetic testing and suggest that increased collaboration between primary care physicians and genetics professionals could benefit patient health care overall.

Table of Contents

List of Tables

List of Figures

Background

The field of genetics is rapidly expanding, resulting in an increasing number of genetic tests available for clinical application. It has been predicted that primary care providers will feel an increased demand to provide information on these newly available genetic tests and their results [1,2,3,4]. Once born, a child first comes into contact with the health care system through his/her primary care provider (PCP). It is known that 3-5% of all children are born with a birth defect [5] and sometimes these birth defects can indicate an underlying genetic condition which should be diagnosed quickly and accurately. A child's pediatrician should refer them to a genetics specialist if a genetic etiology is suspected. Once a patient arrives in a pediatric genetics clinic, an accurate diagnosis is the desired end-point so that families will have correct information about the prognosis, potential treatments and recurrence risk.

We have seen, through our experiences at Children's Memorial Hermann Hospital and Lyndon B. Johnson General Hospital, both in Houston, Texas, that children and adolescents are commonly referred to our genetics clinic upon suspicion of genetic disorders such as Neurofibromatosis type I and Marfan syndrome. However, many of these children have had no work up at all prior to their referral. Patients are also referred with a confirmed diagnosis of Down syndrome, for example, only to find out that they were diagnosed using CMA, when a karyotype is still the 'gold standard' for diagnosis [6].

We propose that diagnosis using non-ideal methods is in part due to a lack of adequate training in genetics in medical schools and pediatrics-based residency programs. There have been several studies performed in the United States, as well as in Europe and Canada, looking at physicians' knowledge of genetics (i.e. inheritance patterns of genetic condition, knowledge about screening for genetic conditions) [7,8,9,10,11,12]. These studies have consistently shown a deficit in knowledge. Many of these studies have focused on cancer genetics knowledge, with few studies focusing on primary care physicians' (PCP) knowledge of which genetic tests are most appropriate in a clinical pediatrics setting.

Thus, in the current study, we aimed to assess how knowledgeable pediatrics-focused residents are about clinical testing, including chromosomal microarray (CMA), in order to highlight specific areas for which current medical school and residency program curricula can be improved. Such improvements will enable physicians to become more comfortable ordering first-tier genetic testing, expedite time to diagnosis and decrease the unnecessary spending of health care dollars by patients and insurance companies.

Since the Human Genome Project's contribution to the knowledge of genetic causes of human diseases, genetics has become a more frequent topic of discussion in mainstream medicine [2]. In less than 10 years since the completion of the project, whole exome sequencing has become clinically available [13]. Now, the thousands of genes in the human genome can be analyzed, often at a lower cost than individual gene analysis. In addition, the rise in popularity of direct-to-consumer (DTC) genetic testing in 2007 [14] has enabled patients to receive personalized genetic testing results without first consulting with their doctor, leaving PCPs and other medical professionals to retroactively interpret the results. Two studies performed in the United States found that 15-19% of PCPs have had at least one patient come to an appointment with questions about personal genomic testing results, that were ordered directly from a DTC company [15,16]. Additionally, the majority of patients who have had DTC testing expect that their doctors will be conversant enough in genetics to be able to explain and interpret the results of that testing [17].

Insufficient Genetics Workforce

Typically, genetic testing, like whole exome sequencing and chromosomal microarray analysis, is ordered by medical geneticists; however the current workforce of genetics professionals is not able to meet demand. The Royal College of Physicians estimated that for every 250,000 people, one full-time geneticist is required [18]. From this report, it has been extrapolated that the United States requires 1,232 full time clinical geneticists for adequate population coverage [19]. According to the American Board of Medical Genetics (ABMG), there are currently a sufficient number of clinical

geneticists to support our population; however the number of clinical geneticists receiving board certification per year has decreased over the last 30 years [20]. Additionally, according to the ABMG 2003 survey of certified geneticists, the majority of clinical geneticists in the United States and in Canada report their practices as nearly full or full, with a little over half being able to accept a new patient within three weeks [21,22]. When stratified by subgroup, half of pediatric geneticists have new patient wait times of up to 3 months and only 5% of pediatric geneticists can see a new patient within one week [23]. Furthermore, 60% of the geneticists surveyed by ABMG feel that the demand for geneticists exceeds the supply. As a follow up to ABMG's 2003 study of the genetics workforce, Cooksey et al., showed that 41% of patients seen by pediatric geneticists require more than one visit to complete a diagnostic evaluation [23]. In order to make the best use of the limited resource of a clinical genetics visit, PCPs could consider ordering first-tier testing so that the results will be available when the patient visits a genetics clinic for the first time.

Genetic Testing

A genetics work-up often includes evaluation of a patient for specific clinical features (e.g. a heart defect or abnormal skin pigmentation) as well as molecular genetic testing. For the purposes of this study, 'first-tier' or baseline testing for clinically-diagnosable genetic conditions aims to rule in or rule out pathognomonic or diagnostic criteria (i.e. Lisch nodules in a patient with suspected Neurofibromatosis type I). Baseline molecular testing includes methodologies such as single gene analysis, karyotype, and Chromosomal Microarray (CMA). Baseline molecular testing also includes methodologies outlined by consensus recommendations. For example, The American College of Medical Genetics (ACMG) currently recommends a 23-mutation panel for use in general population screening for cystic fibrosis [24]. Additionally, the American College of Obstetrics and Gynecology (ACOG) issued a consensus statement in 2011 stating that complete sequencing of the entire *CFTR* gene that is known to cause cystic fibrosis is never appropriate for carrier screening due to the risk of receiving difficult-to-interpret results [25]. Similar statements exist for several of the conditions, such as Fragile X and phenylketonuria, that were chosen as the focus of the current study [26,27].

Specific attention should be paid to the ACMG's recently published guidelines for use of array-based technology [28] as well as the International Standard Cytogenomic Array (ISCA) Consortium's recommendation of array-CGH (chromosomal microarray, CMA) as a first-tier clinical diagnostic test for persons with unexplained developmental disability, autism spectrum disorders, or multiple congenital anomalies [29]. When CMAs were first ordered for the evaluation of microdeletions and microduplications in a patient, a standard karyotype was often concurrently ordered. Today, it is recognized that with the exception of CMA's inability to detect balanced translocations, karyotypes are redundant testing when ordered alongside a CMA. On the other hand, CMAs do not detect point mutations or trinucleotide repeat mutations responsible for the majority of genetic disorders like achondroplasia and Fragile X, respectively. Our experience has been that many health care providers are still ordering a CMA and karyotype together, or are ordering a CMA for single gene disorders, like achondroplasia, that it cannot detect. For this reason, we chose to emphasize CMAs in our study.

Primary Care Providers as Gatekeepers

Primary care providers have first contact with undiagnosed patients and are responsible for continuing to care for patients once they receive a diagnosis. Thus, it has been proposed that PCPs act as gatekeepers to specialists such as medical geneticists [30,31]. Without supplanting the role of genetics professionals, it is crucial to educate PCPs about baseline genetic testing that can be completed prior to a genetics consultation if they are to take on a more active gatekeeper role. Many children are referred to our genetics service with little to no previous work up, meaning they must be seen multiple times before a diagnosis is achieved. This increases the overall cost to families.

Health Care Costs

The case scenarios in our study ask residents to choose the next most appropriate first-tier genetic test/clinical action in conjunction with a referral to a genetics specialist. There are several genetic testing methodologies that can give a

correct diagnosis; however, it would be prudent for physicians to know the methodologies that give the maximum information in the most straight-forward manner for medical management, recurrence risk, and for cost savings purposes.

Many genetic diagnoses can be established by both direct and indirect methods. Obviously, the most direct method early in an individual's evaluation will lead to a reduction in health care costs. In 2009, health care spending in the United States was the highest of all industrialized countries, totaling $2.5 trillion dollars or 17.6% of the nation's Gross Domestic Product (GDP) [32]. Certainly this cost is driven up by duplicate and redundant genetic testing. A case example that we focused on with the current study is the diagnosis of Down syndrome. Students learn through undergraduate genetics courses and/or in medical school that Down syndrome is caused by extra material from chromosome 21. Ninety-five percent of cases of Down syndrome are caused by the sporadic occurrence of an extra chromosome 21 and 3-4% of cases are caused by a translocation involving an extra chromosome 21. Additionally, 1-2% of cases are due to mosaicism [33]. Each genetic cause of Down syndrome has a different recurrence risk [34]. The 'gold-standard' for diagnosis of any aneuploidy, including Down syndrome, is through standard karyotype, enabling differentiation between a free trisomy, a translocation, and mosaicism [6]. There are other genetic testing methodologies, such as fluorescence in-situ hybridization (FISH) or CMA that can be used to make the suspected diagnosis because both confirm the presence of extra material from chromosome 21. However, neither FISH nor a CMA can determine whether the extra chromosome 21 material is from a free trisomy or a translocation [35]. While medical management can be carried out based on FISH or CMA results, the American Academy of Pediatrics recommends that a positive FISH result be confirmed with a karyotype [33].

In summary, there are many methods to determine a diagnosis of Down syndrome, but a karyotype is recommended because it gives the most complete information necessary for accurate characterization of recurrence risk. We specifically included this scenario in our study in order to investigate whether residents are mistakenly ordering incorrect or redundant testing for Down syndrome. There are

several other situations for which redundant testing is frequently ordered so the discussion of Down syndrome can be extrapolated to those as well.

Medical School and Resident Education

To combat increasing health care spending on genetic testing, PCPs must receive more education about genetic testing in medical school and in residency. Several taskforce and work group investigations [4,36,37] have explored the idea that medical schools and residency programs are not preparing PCPs to provide genetic services and information to their patients. While there are numerous articles touting the lack of and need for genetics education in medical schools and residency programs in the U.S. [38], there are recognized obstacles to integrating genetics into medical school and residency program curricula. These obstacles include: a crowded curriculum, lack of knowledgeable faculty, a disconnect between basic sciences and clinical experiences during training, failure to integrate genetics across the curriculum, inadequate representation of genetics on certifying exams, and lack of management and referral guidelines in genetics [39].

The Accreditation Council for Graduate Medical Education (ACGME) is responsible for releasing guidelines by which medical residencies must structure their residency programs. According to ACGME guidelines[40], pediatric residents must complete seven months of subspecialty training and have the option to rotate through genetics among other choices. Thus, at the residency level, genetics is not a required rotation in pediatrics. Additionally, according to ACGME guidelines, genetics is an optional area of study in pediatric neurology and is not mentioned in the guidelines for family practice or pediatric internal medicine residencies [41,42,43]. Without proper training, pediatric-focused PCPs will not be familiar with the appropriate use of basic clinical genetic testing such as karyotypes, FISH, microarray and other molecular testing to evaluate pediatric genetic syndromes.

In order to prepare graduating medical students for applying genetics information to their patients' conditions, medical schools should focus on teaching the clinical application of genetics in addition to basic genetics information including

inheritance patterns. The University of Texas Medical School at Houston (UT) does require their students to take genetics in medical school, although the course is not a semester-long course like many others. Furthermore, genetics is a required two-week rotation in the pediatrics residency program at UT [44]. There are other medical schools, like Baylor College of Medicine, that are beginning to offer special programs or 'tracks' to students interested in genetics. These programs are working to incorporate more genetics into the curriculum for everyone else, too [45,46]. Restructuring medical school curriculum as these programs have done shows potential to integrate more training in genetics into medicine.

Originally, research showed that not only did primary care providers have inadequate genetics education and knowledge, but that they were also reluctant to remedy this problem [47]. However, more recent studies have found that PCPs acknowledge a need to increase their genetics knowledge [36,48]. Several strategies to address these issues have been proposed by PCPs and clinical genetics professionals. These include Continuing Medical Education (CME) courses, lectures, case-based educational material that can be integrated into residency training programs and short internships with genetics professionals. Each solution has advantages and disadvantages that should be explored in order to best suit the needs of PCPs at all levels of training.

Many diseases have a genetic component; as such, it is important for most medical specialties to have some working knowledge of how disease is influenced by genetics. While most children enter a genetics clinic through a referral from their PCP, there must be a balance between under and overeducating these generalists about genetics. Since PCPs do not seem to be adequately educated in the clinical application of genetic testing, how should they proceed when caring for their patients with a suspected genetic disease? Essentially, there are two choices: one, PCPs could order no genetic testing and refer all patients with suspected genetic conditions to medical geneticists. Alternatively, PCPs could continue as they have been, ordering genetic tests in conjunction with a referral to a medical geneticist. There are advantages and disadvantages to both approaches that can be considered separately.

Even in the first scenario where PCPs order no genetic testing but refer instead to a medical geneticist, there is a certain level of basic genetics knowledge needed for PCPs to identify patients who might benefit from such a consult. In this case, a PCP would need to recognize facial and/or body features that might characterize a genetic syndrome. The strategy of referring patients for a genetics consultation will ensure that genetic testing is only ordered by the 'experts', an ideal solution if one only cares to decrease wasteful healthcare spending. However, this strategy will likely necessitate more visits with the genetics team before a diagnosis is reached, placing extra strain on genetics clinics that currently have new-appointment wait times of 3 months or longer [23]. The first visit for these patients will entail an evaluation with ordering of preliminary tests and subsequent visits will be needed for interpretation of the first round of genetic testing and the addition of second-tier testing, when necessary. A problem with the approach outlined above is aforementioned insufficiency of the genetics workforce, such that we will be unable to meet future demands of the population. Furthermore, Huang et al., (2002) found that for children with Williams syndrome, an earlier diagnosis reduced the number of tests necessary for the child's medical care. This decrease in cost is likely due in part to the specific health care guidelines that exist for children with Williams syndrome that allow their medical care to be extremely focused [49]. Reaching a diagnosis in the fewest visits possible is likely to reduce financial burdens on families with children who have genetic conditions.

Alternatively, PCPs could continue ordering genetic testing to the best of their abilities in conjunction with a referral to a genetics specialist. There is evidence, however, that this approach is resulting in increased health care-related costs. ARUP laboratories found that over an eleven-month period in 2010, genetic counselors employed by their laboratory identified and cancelled or changed inappropriately ordered genetic tests, totaling an average of $36,500 per month [50]. Certainly, some of this ordering error could be due to unfamiliarity with test requisition forms, which often vary between laboratories. Additionally, it is not possible to tell if the doctor filled out the requisition form or if it was filled out by a nurse or other employee. Thus, it is conceivable that the correct test was requested by the doctor, but marked incorrectly

on the requisition form by another individual. ARUP also found that 17% of misordered tests were for a cystic fibrosis panel with reflex to full sequencing of the cystic fibrosis gene, *CFTR*. While rare in comparison to many indications for which a child might see a PCP, cystic fibrosis is a common genetic condition among individuals of Caucasian descent, with an incidence of 1 in 2,500. Cystic fibrosis is caused by homozygous mutations in the cystic fibrosis transmembrane conductance regulator protein (*Cftr*) encoded by the *CFTR* gene. One mutation is inherited from each parent that prevents the *Cftr* protein from working correctly leading to a buildup of mucus in the lungs, gastrointestinal, and pancreas of affected patients [51]. Among non-Hispanic Caucasians, 88% of mutations responsible for cystic fibrosis are detected by the 25-common mutation panel recommended by The American College of Medical Genetics (ACMG) [51]. The detection rate is higher among Ashkenazi Jews and lower among individuals of African American or Hispanic American descent. Thus, for most individuals of Ashkenazi Jewish or non-Hispanic Caucasian descent, the common mutation panel, that costs $210 [52], is appropriate and adequately detects most common mutations responsible for cystic fibrosis. In an individual of Hispanic American descent, a healthcare provider might consider ordering full sequencing of the *CFTR* gene to bring the detection rate for mutations up from 57% to 98.7%. The cost of full sequencing however is $1,870. The difference between a common mutation panel and full sequencing might be difficult to appreciate without sufficient background knowledge of genetic testing methodologies and differences in carrier frequencies among various ethnic groups. If PCPs continue to order genetic testing for cystic fibrosis, they must be educated on the suitability of different testing methodologies for different ethnic groups to ensure that ordering of wasteful genetic testing is decreased.

Because it has been suggested by focus groups that case-based genetics education might be a helpful tool to increase knowledge of genetics and genetic testing in primary care [48], the current study aimed to evaluate current knowledge in a subset of pediatric-focused medical residents when given hypothetical clinical scenarios. These scenarios were designed to be representative of common clinical situations that might be encountered by a generalist working with children. We aimed to identify weaknesses, if present, in the current state of clinical genetics testing knowledge as

part of an overall movement to increase the quality of medical services available to the pediatric population.

Materials and Methods

Study Design

The survey-based study was designed to assess the knowledge of first-tier genetic testing among pediatric-focused residents since these are the specialties most likely to encounter a child with an undiagnosed genetic condition. A survey of case-based scenarios was used to assess the current working knowledge of medical residents at The University of Texas Medical School at Houston (UT) and Baylor College of Medicine in four different pediatric-focused residencies. Demographic information was also obtained on the responders. Comparisons were made between residency programs, residency specialties, year of residency, and prior experience and education. We hypothesized that all residents would have a deficit of knowledge with regard to ordering genetic testing as part of a baseline genetics work-up.

Study Population

Residents were recruited for this study from the following pediatric-focused specialties: Categorical Pediatrics, Medicine/Pediatrics (Med/Peds), Pediatric Neurology (Pedi Neuro), and Family Practice. Residents were recruited from all years of residency. Participating institutions were The University of Texas Medical School at Houston (UT) and Baylor College of Medicine (BCM), both in Houston, Texas.

Residents were invited to participate in the study by a series of emails sent over a 4-month period. Data collection was initiated on November 21, 2011, and completed on March 23, 2012. The emails were sent to the residents by their program directors and no identifying information was made available to the primary investigator and committee. The emails included a link to the survey in SurveyMonkey® (Appendix A).

The study was educational in nature, thus it was considered exempt by the Institutional Review Boards (IRBs) at UT (HSC-MS-11-0574) and BCM (H29897). As required by the IRB process, the email sent to the residents included the purpose of the study along with information on the voluntary and anonymous nature of their participation in the study. This information was repeated on the first page of the survey

and participants were asked to consent by clicking that they understood (Appendix B). There was no financial incentive offered for completion of the survey.

The questionnaire included 33 items assessing general demographic information, previous experience with genetics, and prior education, as well as 15 scenario-based questions to assess genetic testing knowledge. Most of the demographic information was collected using multiple choice questions; however, some questions provided areas for free response. Additionally, respondents were given the opportunity to enter comments about the survey upon completion. Each scenario-based question focused on one genetic condition. The genetic conditions were chosen based on those that are commonly seen in genetics clinic as well as on genetic conditions that residents must be familiar with in order to pass their board examinations [53]. The questions were written by the primary investigator and reviewed by the committee. An answer was deemed correct by the investigating committee based on their experience and recommendations from various professional organizations and websites (e.g. ACMG and GeneTests.org). The study did not aim to assess residents' ability to recall a genetic condition based on clinical features. Thus, for some scenarios, the question provided the residents with the suspected diagnosis, enabling them to focus on choosing only the genetic testing needed to confirm the particular diagnosis, as opposed to unnecessarily ordering a full work-up.

For all genetic tests in the survey, prices charged to insurance companies were obtained from the clinical laboratories, hospital, or clinic that offers the tests (Appendix C). When insurance pricing was not available, institutional prices were used. Price information was obtained from the following laboratories, hospitals, and/or clinics: Baylor College of Medicine Medical Genetics Laboratories in Houston, TX; Children's Memorial Hermann Hospital in Houston, TX; City of Hope Molecular Diagnostic Laboratory in Duarte, CA; Esoterix, Inc. in Austin, TX; Fisher Scientific (http://www.fishersci.com); Greenwood Genetic Center in Greenwood, SC; Robert Cizik Eye Clinic in Houston, TX; The Ohio State University Medical Center in Columbus, OH; and the University of Oklahoma Health Sciences Center Genetics Laboratory in Oklahoma City, OK. It was assumed that for each hypothetical patient

scenario, correct genetic testing would have eventually been ordered, even if not a by the primary care provider. Thus, in order to assess the total cost of diagnosis for the hypothetical patient, the price of the correct genetic test was added to all incorrect answer options that did not already include the correct test. Cost analysis was performed for select questions comparing residents who responded correctly to those who responded incorrectly.

Statistical Analysis

Data collected from SurveyMonkey® was exported to Microsoft® Excel and then into STATA®10 (STATA Corporation, College Station, TX) for analysis. All data was analyzed using p values that were significant if < 0.05. Percent score was calculated as the number of questions each respondent got correct out of the total number they answered, regardless of whether they answered all questions. For variables comprised of two groups, t-tests were run to test for significance of effect on overall percent score (H_0 = mean percent score is the same for both groups). For variables comprised of more than two groups, classical one-way ANOVA was run to test for significance of effect on overall percent score (H_0= mean percent score is the same for all groups) with posthoc Tukey tests to identify which group was different, if any. Additionally, percent score was compared between those residents who answered only the first five questions and those residents who answered more than five questions, between residency programs, and between residency specialties. Variables found to be significant by univariate analysis were analyzed using linear regression when appropriate, then examined with multivariate analysis.

Three members of the committee and one outside genetics professional assigned each scenario-based question a value for the expected percentage of residents that should correctly answer the question (expected correct rate). The values were assigned between 0% and 100% in 25% increments. To prevent bias, expected correct rates were determined before these individuals had seen the results of the study. Subsequent analysis of expected correct rates showed raters to be in 'fair' agreement based on Interpretation of Kappa adapted by Viera and Garrett (2005) [54]

(kappa statistic = 0.35). An average of these values (average expected correct rate) was used to run a binomial probability test to determine whether the observed correct rate differed significantly from the expected correct rate.

For each scenario-based question, several variables were tested with chi^2 for association with percent score overall and with correct answer rates per individual question. These variables included general demographics, information about current residency program, educational history, and about residents' families such as the number of children they have and whether anyone in their family had ever been diagnosed with a genetic condition. See Appendix D for a complete listing of variables.

Results

General Demographics and Response Rates

Table 1 summarizes the study population stratified by residency program, residency year, and specialty. At UT, the majority of eligible participants were residents in categorical pediatrics (48.9%, 68 of 139), followed by family practice (25.9%, 36 of 139), medicine/pediatrics (16.5%, 23 of 139), and pediatric neurology (8.6%, 12 of 139). At BCM, the majority of eligible participants were also residents in categorical pediatrics (75.0%, 111 of 148), followed by medicine/pediatrics (20.9%, 31 of 148), then pediatric neurology (4.1%, 6 of 148). Residents from the BCM family practice program never received the invitation to participate in the study. Overall, the majority of eligible participants were residents in categorical pediatrics (62.4%, 179 of 287), followed by medicine/pediatrics (18.8% 54 of 287), then family practice (12.5%, 36 of 287), and finally pediatric neurology (6.3%, 18 of 287).

Of the 287 residents that were eligible to participate in the study, we received responses from 106 individuals giving us a 36.9% percent response rate. Nineteen respondents were excluded from analysis because they did not answer any scenario questions, resulting in a total of 87 respondents. Among the 87 respondents, six more were excluded because they were either not in one of the four residencies examined by this study, no longer in a residency program, or not affiliated with BCM or UT. The final number of respondents analyzed was 81 (28.2% response rate).

Table 1: Study Population Stratified by Residency Program, Residency Year, & Residency Specialty

Program	Year	Pediatrics	Medicine/ Pediatrics	Pediatric Neurology	Family Practice	
UT	PGY-1	22	6	2	12	
	PGY-2	20	4	3	12	
	PGY-3	26	6	3	12	
	PGY-4	0	7	3	0	
	PGY-5	0	0	1	0	
		68	**23**	**12**	**36**	**139**
BCM	PGY-1	36	8	5	n/a	
	PGY-2	35	8	3	n/a	
	PGY-3	40	8	0	n/a	
	PGY-4	0	7	0	n/a	
		111	**31**	**8**	**n/a**	**150**
Totals		**179**	**54**	**20**	**36**	**289**

Table 2 summarizes general demographic information of respondents. The majority (72.8%, n=59) were female, in residency at UT (63.0%, n=51), and had attended medical school in the United States (82.7%, n=67). In addition, the majority of respondents (60.5%, n=49) were younger than 30 years of age. For demographic information collected by free response, investigators analyzed data in groups created after the collection of data was complete (i.e. undergraduate majors were grouped into 'Biology/Health, Other Science, and Liberal Arts categories). When more than one major or minor was listed, respondents were grouped using whichever major or minor theoretically would have given them more instruction in genetics. Most respondents (55.6%, n = 45) majored in a Biology/Health field at their undergraduate institution (e.g. biology, biomedical science, biology and molecular genetics). Most respondents (65.0%, n=53) did not complete a genetics rotation in medical school, although eight respondents (10.0%) elected to complete a genetics rotation in medical school even though it was not required.

Table 2: General Demographic Information of Respondents

Sex	**Number**	**%**
Male	21	25.9
Female	59	72.8
No response	1	1.2
Age		
Younger than 30 years	49	60.5
30-34 years	19	23.5
Older than 34 years	13	16.1
Residency Program		
UT	51	63.0
BCM	30	37.0
Attended Medical School in the US		
Yes	67	82.7
No	14	17.3
Post-call on day of survey		
Yes	11	13.6
No	70	86.4
Undergraduate Major		
Biology/Health	45	55.6
Other Science	12	14.8
Liberal Arts	18	22.3
No response	6	7.4
Undergraduate Minor		
Biology/Health	6	7.4
Other Science	12	14.8
Liberal Arts	14	17.3
No response/No minor	49	60.5
Nature of Genetics Rotation in Medical School		
Elective	8	10
No Rotation	53	65.0
No Response	12	25.0
Total	**81**	

Table 3 summarizes residency information for the 81 respondents analyzed in this study. Most responders were categorical pediatrics residents (63.0%, n=51), followed by family practice (18.5%, n=15), medicine/pediatrics (12.3%, n=10), and finally pediatric neurology (6.17%, n=5). Except for family practice, roughly equal numbers of responses were received from UT and BCM in each specialty. For UT and

BCM, most residents were from categorical pediatrics (n=28 and n=23, respectively). The fewest responders were from pediatric neurology (n=3 and n=2, respectively).

Table 3: Summary of Number of Respondents by Residency Specialty, Year, and Medical School Affiliation

Program	Year	Pediatrics	Medicine/ Pediatrics	Family Practice	Pediatric Neurology	
UT	PGY-1	8	2	8	1	
	PGY-2	10	1	4	1	
	PGY-3	10	2	3	0	
	PGY-4	0	0	n/a	0	
	PGY-5	0	n/a	n/a	1	
	Total	**28**	**5**	**15**	**3**	**51**
BCM	PGY-1	10	2	n/a	1	
	PGY-2	4	2	n/a	1	
	PGY-3	8	1	n/a	0	
	PGY-4	1	0	n/a	0	
	Total	**23**	**5**	**n/a**	**2**	**30**
Totals		**51**	**10**	**15**	**5**	**81**

Table 4 shows response rate by residency year stratified by residency program. The overall response rate for the study was 28% (81/287). The response rate was higher for UT than for BCM (35% vs. 20%) and the response rate was highest among residents in the UT family practice and categorical pediatrics residency programs (42% and 41%, respectively).

Table 4: Response Rates by Residency Year Stratified by Residency Program

Program	Year	Pediatrics	Medicine/ Pediatrics	Family Practice	Pediatric Neurology	
UT	PGY-1	36%	33%	67%	50%	
	PGY-2	50%	25%	33%	33%	
	PGY-3	38%	33%	25	0%	
	PGY-4	n/a	0%	n/a	0%	
	PGY-5	n/a	n/a	n/a	100%	
	Total	**41%**	**22%**	**42%**	**37%**	**35%**
BCM	PGY-1	27%	25%	n/a	25%	
	PGY-2	12%	25%	n/a	50%	
	PGY-3	20%	13%	n/a	n/a	
	PGY-4	n/a	0%	n/a	n/a	
	Total	**20%**	**21%**	**n/a**	**19%**	**20%**
Totals		**31%**	**21%**	**42%**	**28%**	**28%**

Case-Based Scenario Questions

Each scenario was given an expected percent correct rate by the investigators. Because not all respondents completed the entire survey, tables 5, 6, and 7 show summaries of responses by each page of scenario questions. The tables include correct answers, expected and observed correct answer rate, and whether the difference between expected and observed correct answer rate was statistically significant. The correct answer for each question is italicized.

The observed correct rates were significantly lower than expected for the scenarios involving Fragile X syndrome, Down syndrome, carrier screening for cystic fibrosis, Spinal Muscular Atrophy, multiple congenital anomalies, Turner syndrome, PKU and achondroplasia, ($p<0.05$). The observed correct rates for the scenarios diagnosing suspected CF and Marfan syndrome were lower than expected, although not statistically significant. Interestingly, the observed correct rate was higher than

expected for scenarios involving ambiguous genitalia, Prader Willi syndrome, Noonan syndrome, unspecified hemoglobinopathy, and Neurofibromatosis type I, although these values were not statistically significant.

Table 5: Observed and Expected Correct Answer rates for Questions 1-5

Q1: Ambiguous Genitalia	**Freq.**	**%**	**Expected Correct Rate**	**P value**
CMA only	0	0.0%		
CMA + Karyotype	6	7.4%		
CAH biochemical screen	8	9.9%		
CAH biochemical screen + Karyotype	47	58.0%	56.3%	0.666
CAH biochemical screen + Karyotype + CMA	20	24.7%		
Q2: Fragile X				
CMA only	5	6.2%		
CMA + Fragile X testing	30	37.0%		
CMA + Fragile X testing + karyotype	15	18.5%		
CMA + karyotype	2	2.5%		
Fragile X testing only	29	35.8%	57.5%	**<0.001**
Q3: Down syndrome				
CMA only	8	9.9%		
FISH for chromosome 21	19	23.5%		
Karyotype only	24	29.6%	62.5%	**<0.001**
CMA + FISH for chromosome 21	22	27.2%		
CMA + Karyotype	8	9.9%		
Q4: New baby suspected CF				
CFTR deletion testing	9	11.1%		
CFTR full sequencing	7	8.6%		
CFTR mutation panel	47	58.0%	57.5%	0.580
CMA	4	4.9%		
CMA + CFTR mutation panel	14	17.3%		
Q5: CF screening with known mutation in a partner				
CFTR deletion testing	3	3.7%		
CFTR sequencing	17	21.0%		
Targeted CFTR for deltaF508	25	30.9%		
CFTR mutation panel	33	40.7%	51.3%	**0.037**
CMA	3	3.7%		
Total (for each question)	**81**			

Table 6: Observed and Expected Correct Answer Rates for Questions 6-10

Q6: SMA	Freq.	%	Expected Correct Rate	P value
Deletion/Duplication testing SMN1	27	37.5%		
CMA	21	29.2%		
Sequencing of SMN1 (all exons)	13	18.1%		
Sequencing of SMN1 (exons 7 and 8 only)	7	9.7%		
Deletion/Duplication SMN1 (exons 7 and 8)	4	5.6%	26.3%	**<0.001**
Q7: Prader Willi syndrome				
CMA	12	16.7%		
FISH for PWS critical region	14	19.4%		
Methylation studies of PWS critical region	24	33.3%	32.5%	0.614
Sequencing of SNRPN	4	5.6%		
UPD testing for PWS critical region	18	25.0%		
Q8: Multiple congenital anomalies of unknown etiology				
CMA	40	55.6%	75.0%	**<0.001**
Karyotype only	2	2.8%		
Fragile X testing	6	8.3%		
Metabolic work-up (PAA, UOA, ACP)	24	33.3%		
Telomere FISH	0	0.0%		
Q9: Turner syndrome				
CMA only	14	19.4%		
Karyotype only	36	50.0%	73.8%	**<0.001**
Skeletal survey	9	12.5%		
Metabolic work-up (PAA, UOA, ACP)	12	16.7%		
Telomere FISH	1	1.4%		
Q10: PKU				
Plasma amino acids + serum PAH	10	13.9%		
Immediately refer to metabolic center	5	6.9%	56.3%	**<0.001**
Sequencing of PAH and switch to low Phe diet	8	11.1%		
Repeat NBS and switch to low Phe diet	15	20.8%		

Low Phe diet + plasma A.A. + repeat NBS	34	47.2%		
Total (for each question)	**72**			

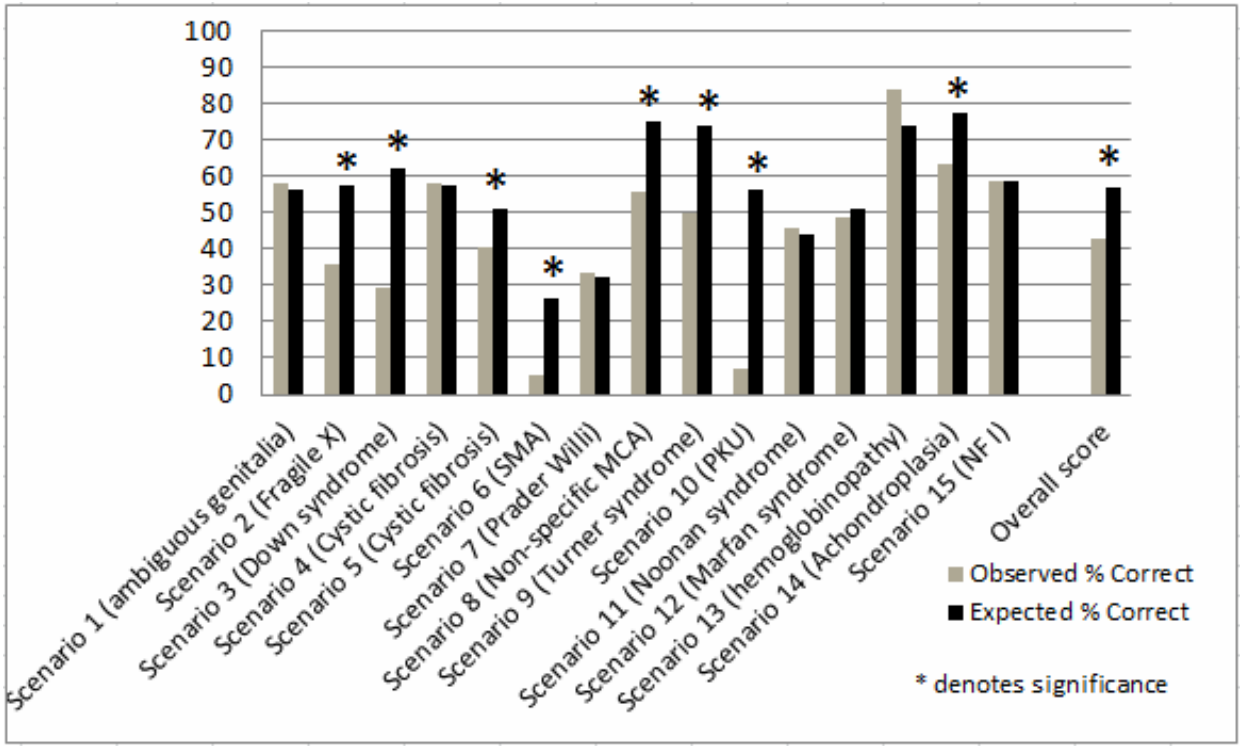
Table 7: Observed and Expected Correct Answer Rates for Questions 11-15

Q11: Noonan syndrome	**Freq.**	**%**	**Expected Correct Rate**	**P value**
CMA only	12	17.6%		
Karyotype for Noonan syndrome	18	26.5%		
Karyotype for Turner syndrome	7	10.3%		
Molecular testing for Noonan syndrome	31	45.6%	43.8%	0.667
Molecular testing for Turner syndrome	0	0.0%		
CMA only	12	17.6%		
Q12: Marfan syndrome				
CMA	3	4.4%		
Echocardiogram, ophthalmologic exam, homocystine & methionine panel	33	48.5%	51.3%	0.371
Metabolic workup (PAA, UOA, ACP)	3	4.4%		
Echocardiogram + ophthalmologic exam	28	41.2%		
RET sequencing responsible for MEN2	1	1.5%		
Q13: Unspecified hemoglobinopathy				
CMA	2	2.9%		
Sequencing FVIII and FIX responsible for hemoglobin A and B	4	5.9%		
Sequencing of HBB gene responsible for sickle cell	4	5.9%		
Hemoglobin electrophoresis, if not already done	57	83.8%	73.8%	0.983
Order sickledex if not already done	1	1.5%		
Q14: Achondroplasia				
CMA	15	22.1%		
Metabolic work up (PAA, UOA, ACP)	1	1.5%		
Serum calcium	3	4.4%		
Skeletal survey	43	63.2%	77.5%	**0.005**
Vitamin D studies	6	8.8%		
Q15: Neurofibromatosis type I				
Diagnose NF1 based on clinical criteria	40	58.8%	58.8%	0.551
Diagnose NF1 after molecular testing is positive	13	19.1%		
Diagnose NF1 after skin biopsy studies are positive	12	17.6%		
CMA	3	4.4%		

Echocardiogram	0	0.0%		
Total (for each question)	**68**			

Figure 1 represents the expected vs. observed score for all 15 case-based scenario questions. There were eight questions for which residents scored significantly lower than expected (as indicated with an asterisk).

Figure 1: Expected vs. Observed Score by Scenario



Overall Score

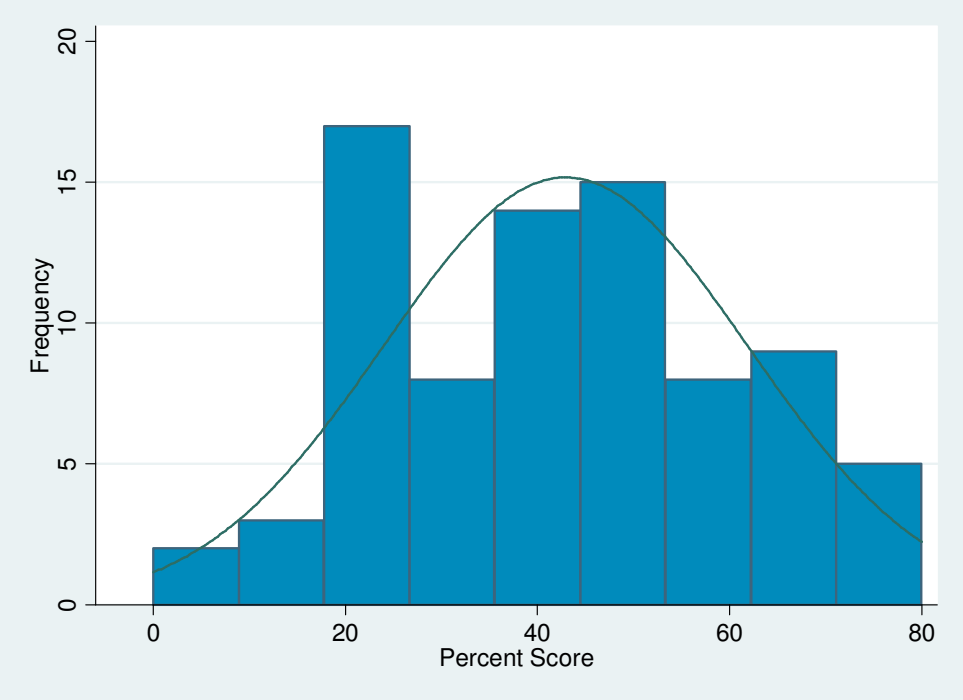
Figure 2 shows the normal distribution of overall score for all respondents (n = 81; p value for skewness = 0.996). The mean overall score was 43.0% (max score = 80%, min score = 0%, SD = 18.9%), which was significantly lower than the expected mean overall score of 56.9% ($p<0.00001$). Table 8 shows scores for all respondents grouped in 20 percent intervals. The majority of respondents received a score of < 60%.

Table 8: Overall Percent Score

Score Groups	% (# of respondents)
<20%	6.17 (5)
20-39%	30.86 (25)

40-59%	35.8 (29)
60-79	22.22 (18)
=80%	4.94 (4)

Figure 2: Overall Percent Score – All respondents



There were several variables that significantly affected the observed mean overall score: number of pages complete, residency specialty, location of medical school, nature of genetics instruction in medical school, and electing to complete a genetics rotation in medical school.

<u>Number of Case-Based Scenario Questions Answered</u>

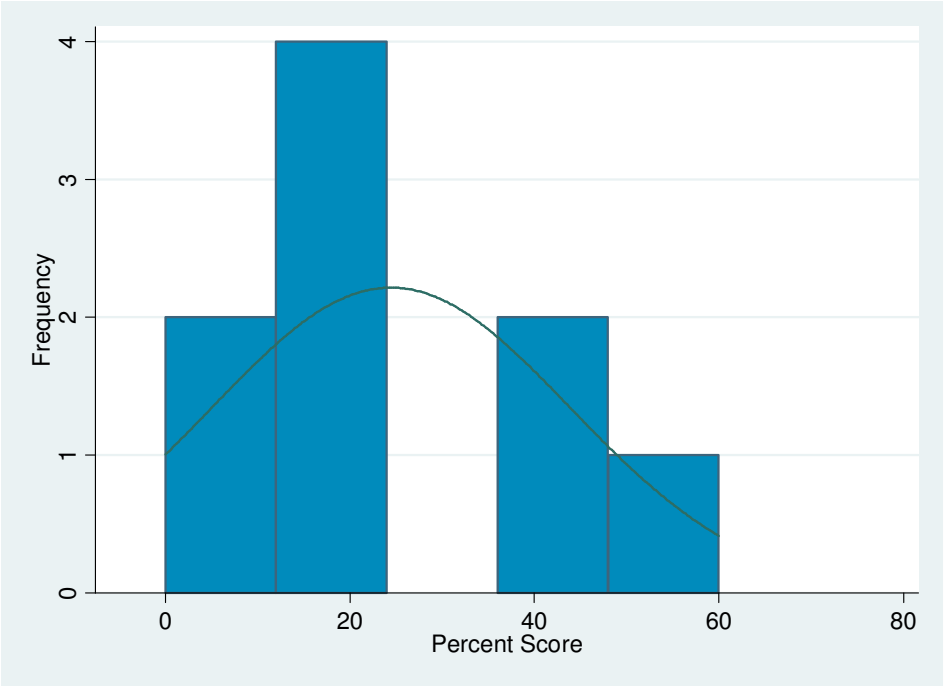
All respondents were grouped according to the number of pages of case-based scenario questions they answered; either 5 (Page 1 only), 10 (Page 1 and 2 only) or 15 (all three pages). Overall, the percent score was different between these groups (ANOVA p value=0.0023) (Table 9). Posthoc Tukey test demonstrated a significant difference in mean score between those who only answered one page and those who completed all three pages. Additionally, linear regression model demonstrated an average increase of 11% in percent score for each additional page completed ($p<0.0005$). There was a significant difference in overall percent score between those who completed only the first page and those who completed all three pages (Table 9).

Table 9: Comparison Overall Score: Number of Pages Completed

# Pages Complete	N	Mean Percent Score	Std. Dev.	P value*
1	9	24.4%	19.4%	**0.001**
2	4	32.5%	17.1%	
3	68	46.0%	17.5%	
*comparing 1 page completed to 3 pages completed				

Figure 3 shows percent score for those who only answered the first five questions (N = 9, p value for skewness = 0.856, mean score = 24.4% (SD = 19.4), min score = 0%, max score = 60%).

Figure 3: Overall Score: One Page Completed (n=9)



The nine individuals who answered only the first page and the four individuals who answered pages 1 and 2 were excluded in Figure 4, which shows the normal distribution of overall score for those respondents who answered all questions (n = 68;

p value for skewness = 0.554). The mean score for this group was 46.0% (max score = 80%, min score = 13.3%, SD = 17.5%).

Figure 4: Overall Score: All Pages Answered (n=68)

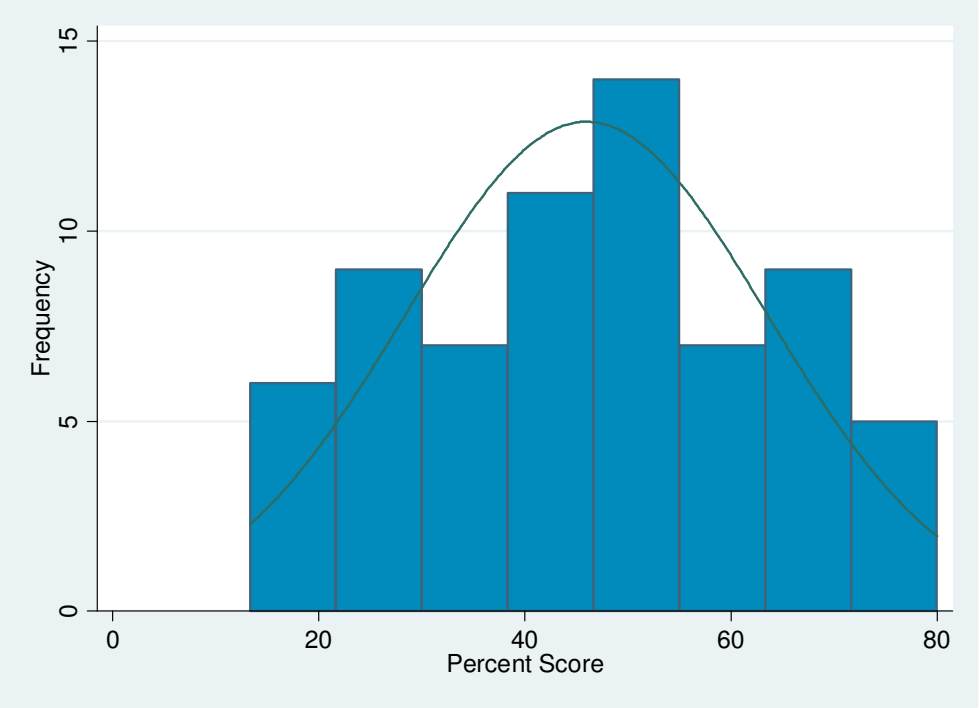


Table 10 shows observed and expected percent correct rate for the first five scenarios for those individuals who only answered questions 1-5 compared to those who answered either 10 or 15 questions. Among these questions, only the new baby with suspected CF question showed a significant difference in correct response rate between these two groups (22.2% correct versus 60.3% correct, p=0.031). However collectively, residents who only completed the first five questions had a significantly lower overall score on those questions than residents who completed all three pages (24.4% vs. 46.8%, p=0.024).

Table 10: Comparison of Score, First 5 pages: One page vs. Three pages complete

	Correct Answer Rate n (%)		P value
	All pages n= 68	**First Page Only n= 9**	
Q1: Ambiguous Genitalia			
CAH biochemical screen + Karyotype	41 (60.3)	3 (33.3)	0.161
Q2: Fragile X			
Fragile X testing only	25 (36.8%)	1 (11.1%)	0.130
Q3: Down syndrome			
Karyotype only	21 (30.9%)	3 (33.3%)	0.883
Q4: new baby suspected CF			
CFTR mutation panel	41 (60.3%)	2 (22.2%)	**0.031**
Q5: CF screening with known mutation in a partner			
CFTR mutation panel	31 (45.6%)	2 (22.2%)	0.188
Mean overall score for first five question	**46.8%**	**24.4%**	**0.024**

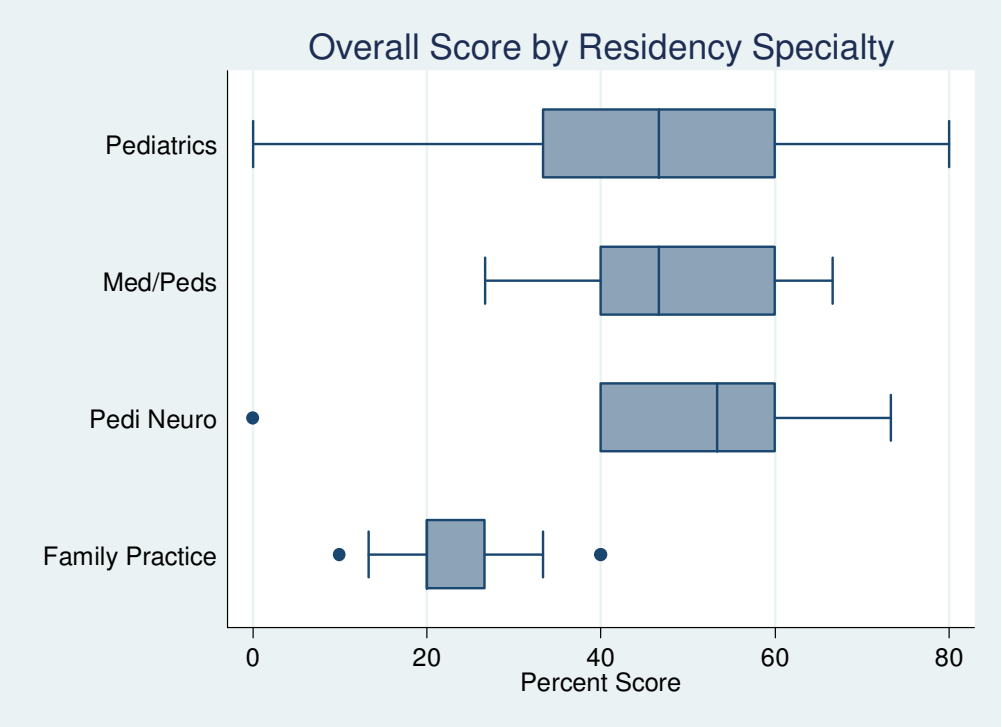
Residency Specialty

As previously stated, the majority of the respondents (n=51) were categorical pediatric residents. There were approximately equal numbers of Med/Peds (n=10) and Family Practice residents (n=15). Pedi Neuro residents accounted for the fewest number of respondents (n=5). ANOVA comparing mean percent score for these four groups resulted in a significant difference in means ($p<0.00001$). Post-hoc tests showed that family practice residents had significantly lower mean scores than all other groups and that the other three groups did not differ significantly from each other. While all groups scored lower than expected (56.9%), overall percent score was only significantly lower than expected for Pediatrics and Family Practice Residencies (Table 11). The distribution of overall score by residency specialty is illustrated in Figure 5.

Table 11: Comparison of Mean Score: Residency Specialty

	n	Mean percent score	Standard deviation	P value (ANOVA)
Pediatrics	51	47.5%*	17.7%	**<0.00001**
Med/Peds	10	48.0%	13.6%	
Pedi Neuro	5	45.3%	28.0%	
Family Practice	15	23.1%*	8.0%	
Total	**81**			
*Significantly lower than overall expected score (56.9%)				

Figure 5: Comparison of Mean Score: Residency Specialty



Residency Year

Overall percent score was also divided into 5 groups by residency year. One-way ANOVA showed that percent score overall did not differ significantly by residency year. However, a trend of increasing percent score with increasing residency year was

observed. With the exception of the one PGY4 and one PGY5 residents, all scores were lower than expected and the scores for PGY1 and PGY2 were significantly lower (Table 12).

Table 12: Comparison of Mean Score: Residency Year

Residency Year	N	Mean score	Std. Dev.	P value (ANOVA)
PGY1	32	40%*	19%	0.417
PGY2	23	42%*	20%	
PGY3	24	47%*	17%	
PGY4	1	60%	n/a	
PGY5	1	60%	n/a	
Total	**81**			
*Significantly lower than overall expected score (56.9%)				

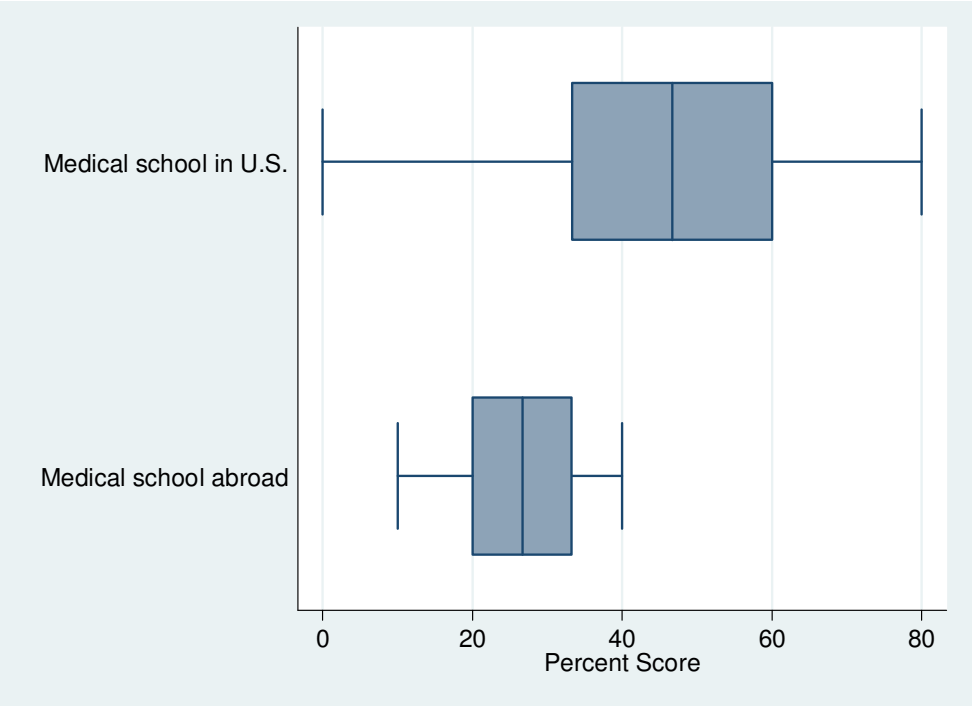
Medical School Location – US versus Abroad

Table 13 shows that the majority of residents attended medical school in the U.S. (82.7%, n=67). Fourteen residents attended medical school abroad. A t-test comparing the mean overall score between these two groups showed that residents who attended medical school in the U.S. scored significantly higher overall than those who attended medical school in another country (Figure 6, $p<0.00001$). However, a one-group t test comparing mean overall score for each group to the expected overall score showed that both groups of residents scored significantly lower than expected (Table 13). Figure 6 is a graphical representation of the information in Table 13.

Table 13: Comparison of Mean Score: Medical School Location

Location of Medical School	N	Mean percent score	Std. Dev.	P value (ANOVA)
U.S.	67	46.7%*	18.3%	**<0.00001**
Abroad	14	25.0%*	9.5%	
Total	**81**			
*Significantly lower than expected overall (56.9)				

Figure 6: Comparison of Mean Score Overall: Medical School Location



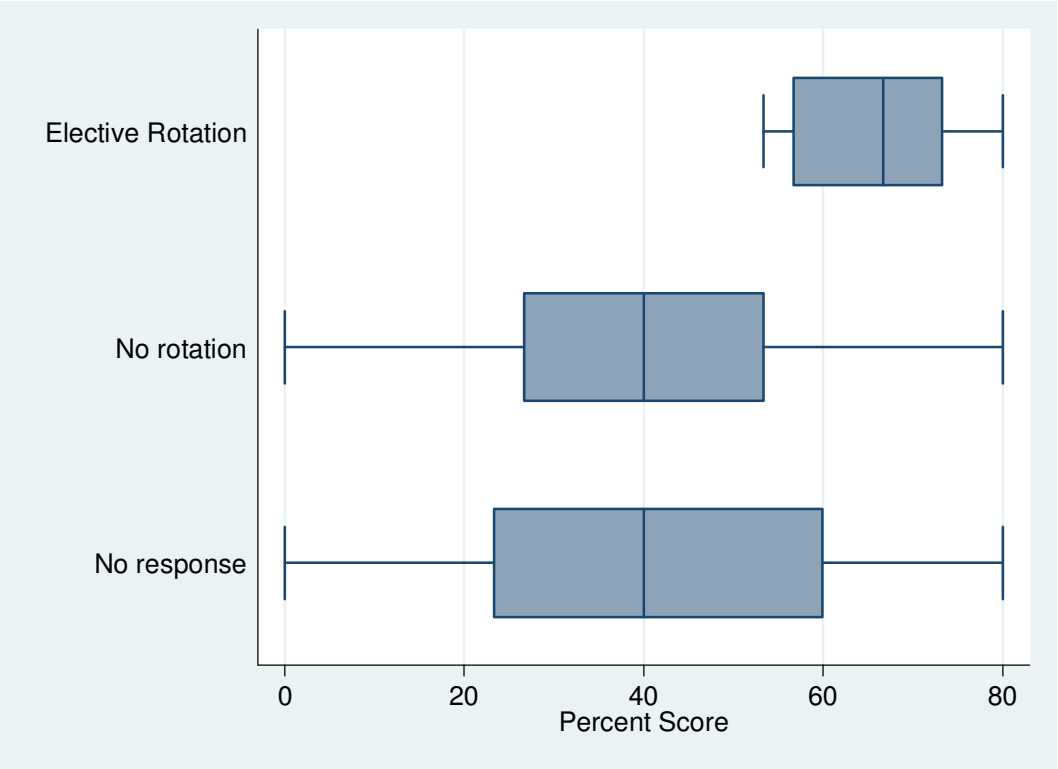
Medical School Genetics Rotation

The majority of the respondents (n=53) reported not completing a genetics rotation during medical school. Eight residents reported that they elected to complete a genetics rotation while in medical school (n=8) while 20 residents did not provide a response to this question. ANOVA comparing the three groups resulted in a significant difference in mean overall percent score (p=0.001) (Table 14). T-tests demonstrated that the respondents taking an elective genetics rotation scored significantly higher than both other groups (p= 0.0001, elective compared to no rotation; p=0.0035, elective compared to no response) and that there was no significant difference in mean score between the no rotation and no response groups (p=0.830). Not only did the residents who elected to complete a genetics rotation in medical school score significantly better than the other two groups, but they also scored significantly higher than expected overall (65.8% vs. 56.9%, p=0.045). Overall percent scores for the residents who reported they did not complete an elective rotation and for those residents who did not provide a response were significantly lower than expected overall. Figure 7 is a graphical representation of the information in Table 14.

Table 14: Comparison of Mean Score: Nature of Medical School Genetics Rotation

Elective Genetics Rotation in Medical School?	N	Mean percent score	Std. Dev.	P value (ANOVA)
Yes	8	65.8	10.4%	0.001
No	53	40.7*	16.5%	
No response	12	39.7*	21.9%	
Total	**81**			
*Significantly lower than overall expected score (56.9%) Significantly higher than overall expected score				

Figure 7: Comparison of Mean Score: Nature of Medical School Genetics Rotation



Medical School Genetics Curriculum

An examination of overall percent score also revealed that the 39 residents who received genetics in a dedicated class in medical school scored significantly higher than the 36 residents who received genetics integrated across their entire curriculum (p=0.049). As seen in Table 15, the overall mean score for those residents who learned

about genetics in a dedicated class was 47.6% compared to the overall mean score of 38.8% for those residents who learned genetics in an integrated format.

Table 15: Comparison of Mean Score: Nature of Genetics Class in Medical School

Nature of Genetics Class	n	Mean Score	Std. Dev.	P value (ANOVA)
Dedicated Class	39	47.6*	17.4%	**0.049**
Integrated Class	36	38.8*	20.8%	
Total	**75**			
*Significantly lower than overall expected score (56.9%)				

The following variables were also examined but were not found to significantly affect overall percent score: gender, medical school residency affiliation, whether or not the residents were post-call, college undergraduate major or minor, whether or not genetics was taken in college undergraduate, number of children or children under 5, family history of a genetic condition, length of medical school genetics rotation, and whether or not residents seek out genetics information via news stories or journal articles.

Multivariate analysis

The four variables which significantly affected overall score (residency specialty, medical school location, nature of medical school genetics class, and nature of medical school genetics rotation) were entered into multivariate analysis. When considered together, only residency specialty and nature of medical school genetics rotation significantly affected overall score (adjusted R-squared: 0.331). Family practice residents scored 19.7% lower on average (p=0.042) than categorical pediatric residents. The 53 residents who indicated that they did not elect to complete a genetics rotation scored 20.0% lower on average (p=0.002) than residents who chose to complete a genetics rotation in medical school.

Redundant and Incorrect Testing Methodologies

There were three scenarios in the survey that gave residents the option to choose redundant genetic testing – scenario 1 (ambiguous genitalia), scenario 2

(Fragile X), and scenario 3 (Down syndrome). Since all 81 respondents completed the three scenarios, there were 243 responses of any type (A, B, C, D, or E). Across all three scenarios, residents chose redundant genetic testing 30.0% of the time (Table 16).

Table 16: Redundant Genetic Testing Responses

Scenario	Redundant Answer Choices	Answer Count
1: Ambiguous Genitalia	B. CMA + Karyotype	6
	D. CAH biochemical screen + Karyotype + CMA	20
2: Fragile X	C. CMA + Fragile X testing + karyotype	15
	D. CMA + karyotype	2
3: Down syndrome	D. CMA + FISH for chromosome 21	22
	E. CMA + Karyotype	8
Total Redundant Answers		**73**

Additionally, seven scenarios contained answer choices that would not diagnose the genetic condition in question. The conditions featured in these scenarios were Fragile X, SMA, Noonan syndrome, Marfan syndrome, hemoglobinopathy, achondroplasia and NF1. Eighty-one respondents answered scenario 2 (Fragile X), 72 respondents answered scenario 6 (SMA), and 68 respondents answered each of the last five scenarios (Noonan, Marfan, hemoglobinopathy, achondroplasia and NF1), giving a total of 493 possible responses of any type to these questions. When totaled, residents ordered genetic testing using the wrong methodology 25.6% of the time (Table 17).

Table 17: Wrong Methodology Testing Responses

Scenario	Answer Choices Featuring Incorrect Methodology	Answer Count
2: Fragile X	CMA	5
	CMA + Fragile X testing	30
	CMA + Fragile X testing + karyotype	15
	CMA + karyotype	2
6. SMA	CMA	21
11. Noonan syndrome	CMA only	12
	Karyotype for Noonan syndrome	18
12: Marfan syndrome	CMA	3
13: Unspecified hemoglobinopathy	CMA	2
14: Achondroplasia	CMA	15
15: NF type I	CMA	3
Total Incorrect Methodology Answer Choices		**126**

Cost Analysis

Analysis of health care dollars was performed for select survey questions (Table 18).

Table 18: Cost Analysis for Select Scenarios

Scenario		Freq (%)	Total Cost* ($)	P value
1. Ambiguous Genitalia	Wrong Choices (A, B, C, & E)	34 (42.0)	2,641.75	**<0.00001**
	Correct Choice (D)	47 (58.0)	861.75	
2. Fragile X	Wrong Choices (A, B, C, & D)	52 (64.2)	2,411.92	**<0.00001**
	Correct Choice (E)	29 (35.8)	390.00	
3. Down syndrome	Wrong Choices (A, B, D, & E)	57 (70.4)	2,275.97	**<0.00001**
	Correct Choice (C)	24 (29.6)	740.00	
8. Multiple Congenital Anomalies	Wrong Choices (B, C, D, & E)	32 (44.4)	2,498.63	**<0.00001**
	Correct Choice (A)	40 (55.6)	1,780.00	
* Mean total cost except Ambiguous Genitalia, where median was reported				

For all four scenarios, the average cost of diagnosis was significantly higher than necessary when respondents answered incorrectly. For example, in the case of Fragile X in scenario 2, the price of correct answer choice E, trinucleotide repeat analysis by DNA Southern Blot for *FMR1,* is $390 with a >99% detection rate. The other answer choices for this scenario contain either unnecessary extra testing (choice B, CMA + Fragile X DNA analysis) or methodologies not able to detect the condition (choice D, CMA +Karyotype) and all cost significantly more than $390.

Variables Affecting Percent Score

Several variables were tested as possible confounders on correct response rate and Table 19 lists them along with the scenarios they influenced, as indicated by an 'X'($p<0.05$). Of the 15 scenarios, 9 had at least one variable that significantly influenced the observed percent correct rate. There were several variables that only affected the correct response rate for one scenario. Residency specialty was found to be significant for five of the scenarios, while location of medical school, nature of genetics rotation in medical school, and number of children affected the correct response rate for three scenarios.

Table 19: Variables Affecting Correct Response Rate by Scenario

	Ambiguous Genitalia	Fragile X	Down syndrome	New baby suspected CF	MCA	Noonan	Hemoglobinpathy	Achondroplasia	NF1
Sex (Male/Female)							X		
Residency Specialty	X				X	X	X	X	
Residency Year	X								
Undergraduate Major									X
Med school in the U.S. or abroad						X	X		
Do you seek out genetic information (e.g. news stories, documentaries)						X			
Genetics class in undergrad		X							
Nature of genetics rotation in medical school			X	X					
Number of children								X	X

Ambiguous Genitalia

Table 20: Correct Responses (%) by Residency Specialty – Ambiguous Genitalia

	Pediatrics	Med/Peds	Pedi Neuro	Family Practice	Total
Wrong	16 (31.4)	3 (30.0)	5 (100.0)	10 (66.7)	**34 (42.0)**
Correct	35 (68.6)	7 (70.0)	0 (0.0)	5 (33.3)	**47 (58.0)**
Total	**51**	**10**	**5**	**15**	**81**

For scenario 1 (ambiguous genitalia), residency specialty and residency year significantly affected the correct answer rate. Med/Peds and categorical pediatric residents had the highest correct answer rates, (70% and 68.6%, respectively), while pediatric neurology had the lowest correct answer rate (0%) (Table 20).

Table 21: Correct Responses (%) by Residency Year – Ambiguous Genitalia

	PGY1	PGY2	PGY3	PGY4	PGY5	Total
Wrong	13 (40.6)	15 (65.2)	5 (20.8)	0 (0%)	1 (100)	**34 (42.0)**
Correct	19 (59.4)	8 (34.8)	19 (79.2)	1 (100)	0 (0%)	**47 (58.0)**
Total	**32**	**23**	**24**	**1**	**1**	**81**

Table 21 demonstrates that the correct response rate dipped initially from year 1 of residency to year 2, but then increased through year 4. However, the correct response rate was 0% in year 5.

Fragile X

Table 22 Correct Responses (%) by Whether Genetics Was Taken in College – Fragile X

	Yes	No	Total
Wrong	43 (70.5)	9 (45)	**52 (64.2)**
Correct	18 (29.5)	11 (55.0)	**29 (35.8)**
Total	**61**	**20**	**81**

Table 23 Correct Responses (%) by Number of College Genetics Classes College – Fragile X

	No genetics classes	1-2 genetics classes	3-4 genetics classes	Total
Wrong	9 (45.0)	41 (70.7)	2 (66.7)	**52 (64.2)**
Correct	11 (55.0)	17 (29.3)	1 (33.3)	**29 (35.8)**
Total	**20**	**58**	**3**	**81**

For scenario 2 (Fragile X), Table 22 shows that residents who took genetics as an undergraduate student (n=61) were more likely to get the question incorrect than those who did not take genetics during their undergraduate studies (n=20). However, even though it was not statistically significant, those residents who took 3-4 genetics

classes in college were less likely to get the question wrong than those who took 1-2 classes (Table 23).

Down syndrome

Table 24: Correct Responses (%) by Nature of Medical School Genetics Rotation – Down syndrome

	Required	Elective	Neither	Total
Wrong	8 (80.0)	2 (25.0)	39 (76.5)	**49 (71.0%)**
Correct	2 (20.0)	6 (75.0)	12 (25.5)	**20 (29.0%)**
Total	**10 (100.0%)**	**8 (100.0%)**	**51 (100.0%)**	**69**

For scenario three (Down syndrome), residents who elected to complete a genetics rotation in medical school were more likely to get the question correct than those who completed one because they were required to and those who did not complete one at all (Table 24). Residents who did not complete a genetics rotation were about as likely to get the question correct as those who completed a genetics rotation because they were required to (25.5% correct vs. 20.0% correct, respectively).

New Baby with Suspected CF

Table 25: Correct Responses (%) by Nature of Medical School Genetics Rotation – New Baby, Suspected CF

	Required	Elective	No rotation	Total
Wrong	6 (60.0)	0 (0.0)	22 (43.1)	**28 (40.6)**
Correct	4 (40.0)	8 (100.0)	29 (56.9)	**41 (59.4)**
Total	**10**	**8**	**51**	**69**

For scenario four (new baby with suspected CF), all residents who completed an elective genetic rotation in medical school answered the question correctly. Residents in the other two categories were about as likely to get the question correct as they were to get it incorrect (Table 25).

Multiple Congenital Anomalies

Table 26: Correct Responses (%) by Residency Specialty - MCA

	Pediatrics	Med/Peds	Pedi Neuro	Family Practice	Total
Wrong	15 (33.3)	4 (40.0)	2 (50.0)	11 (84.6)	**32 (44.4)**
Correct	30 (66.7)	6 (60.0)	2 (50.0)	2 (15.4)	**40 (55.6)**
Total	**45**	**10**	**4**	**13**	**72**

For scenario 8 (MCA), table 26 shows that the percent correct rate was largely the same, ranging from 50 to 67% for all specialties except family practice, whose correct rate was 15.4%.

Noonan syndrome

Table 27: Correct Responses (%) by Residency Specialty - Noonan

	Pediatrics	Med/Peds	Pedi Neuro	Family Practice	Total
Wrong	19 (44.2)	8 (80.0)	0 (0.0)	10 (90.9)	**37 (54.4)**
Correct	24 (55.8)	2 (20.0)	4 (100.0)	1 (9.1)	**31 (45.6)**
Total	**43**	**10**	**4**	**11**	**68**

Table 27 demonstrates that for scenario 11 (Noonan syndrome), 100% of residents in pediatric neurology got the question correct; while family practice had the lowest correct rate (9.1%). Pediatrics had the second highest correct rate (55.8%) and med/peds had the third highest (20%).

Table 28: Correct Responses (%) by Whether Medical School was Attended in the U.S. - Noonan

	Medical School in the U.S.	Medical School Abroad	Total
Wrong	28 (48.3)	9 (90.0)	**37 (54.4)**
Correct	30 (51.7)	1 (10)	**31 (45.6)**
Total	**58**	**10**	**68**

Table 29: Correct Responses (%) by Whether Residents Seek out Genetics Information - Noonan

	Yes	No	Total
Wrong	7 (35.0)	30 (62.5)	**37 (54.4)**
Correct	13 (65.0)	18 (37.5)	**31 (45.6)**
Total	**20**	**48**	**68**

Table 28 shows that the majority of residents who attended medical school outside of the United States answered the question about Noonan syndrome incorrectly, while residents who attended medical school in the United States were about as equally likely to answer the question incorrectly as they were to answer it correctly. Additionally, residents who reported that they seek out genetics information were more likely to get the question about Noonan syndrome testing correct than those who did not report this (Table 29).

Unspecified Hemoglobinopathy

Table 30: Correct Responses (%) by Gender - hemoglobinopathy

	Male	Female	Total
Wrong	6 (31.6)	5 (10.4)	**11 (16.4)**
Correct	13 (68.4)	43 (89.6)	**56 (83.6)**
Total	**19 (28.4)**	**48 (71.6)**	**67**

For the scenario about an unspecified hemoglobinopathy, female residents were more likely than males to answer correctly (Table 30).

Table 31: Correct Responses (%) by Residency Specialty - hemoglobinopathy

	Pediatrics	Med/Peds	Pedi Neuro	Family Practice	Total
Wrong	3 (7.0)	2 (20.0)	0 (0.0)	6 (54.6)	**11 (16.2)**
Correct	40 (93.0)	8 (80.0)	4 (100.0)	5 (45.5)	**57 (83.8)**
Total	**43 (63.2)**	**10 (14.7)**	**4 (5.9)**	**11 (16.2)**	**68**

For scenario 13 (hemoglobinopathy), 100% of pediatric neurology residents answered correctly. Med/Peds and Pediatrics had similar, high correct response rates

(80% and 93%, respectively). Family practice residents had the lowest correct rate (45.5%), (Table 31).

Table 32 Correct Responses (%) by Whether Medical School was Attended in the U.S. - Hemoglobinopathy

	Medical School in the U.S.	Medical School Abroad	Total
Wrong	6 (10.3)	5 (50.0)	**11 (16.2)**
Correct	52 (89.7)	6 (50.0)	**57 (83.8)**
Total	**57**	**11**	**68**

Additionally, for the hemoglobinopathy scenario, residents who went to medical school in the U.S. had a higher correct response rate (89.7%) than those who went to medical school outside of the U.S. (54.6%), as seen in Table 32.

Achondroplasia

Table 33: Correct Responses (%) by Residency Specialty - Achondroplasia

	Pediatrics	Med/Peds	Pedi Neuro	Family Practice	Total
Wrong	15 (34.9)	2 (20.0)	0 (0.0)	8 (72.7)	**25 (36.8)**
Correct	28 (65.1)	8 (80.0)	4 (100.0)	3 (27.3)	**43 (63.2)**
Total	**43**	**10**	**4**	**11**	**68**

For scenario 14 (achondroplasia), Table 33 shows that residents in pediatric neurology had a 100% correct response rate, followed by med/peds (80%), then pediatrics (65%). Family Practice had the lowest correct response rate (27.3%).

Table 34: Number of Correct Responses (%) by Number of Children - Achondroplasia

	No children	1 child	2 children	Total
Wrong	23 (45.1)	2 (25.0)	0 (0.0)	**25 (36.8)**
Correct	28 (54.9)	6 (75.0)	9 (100.0)	**43 (63.2)**
Total	**51**	**8**	**9**	**68**

Table 34 shows that percent correct rate increased with increasing number of children. Respondents with 2 children (n=9) had a 100% correct response rate for the

scenario involving achondroplasia, while residents with no children were about equally as likely to answer the question correctly as incorrectly.

Neurofibromatosis Type 1

Table 35: Correct Responses (%) by Undergraduate Major – NF1

	Bio/Health	Other Science	Liberal Arts	Total
Wrong	10 (25.6)	9 (66.7)	9 (56.3)	**25 (39.1)**
Correct	29 (74.4)	3 (33.3)	7 (43.8)	**39 (60.9)**
Total	**39**	**9**	**16**	**64**

Table 36: Correct Responses (%) by Number of Children – NF1

	No Children	1 Child	2 Children	Total
Wrong	19 (37.3)	7 (87.5)	2 (22.2)	**28 (41.2)**
Correct	32 (62.8)	1 (12.5)	7 (77.8)	**40 (58.8)**
Total	**51**	**8**	**9**	**68**

Table 35 shows that for scenario 15 (NF1), residents with a biology/health undergraduate major had the highest correct response rate (74.4%). Interestingly, residents with a liberal arts major had a higher correct response rate than residents with a major in sciences other than biology (43.8% vs. 33.3%, respectively). Residents with one child had the lowest correct response rate (12.5%), while residents with two children had the highest (77.8%) as seen in Table 36.

Discussion

This study was undertaken to evaluate the baseline genetic testing knowledge among a selected group of pediatric residents in Houston, Texas. Similar to other studies of resident knowledge, we found that residents in these pediatric-focused residency programs had insufficient knowledge of first-tier genetic testing. The mean overall score was 43.0%, (maximum score of 80% and a minimum score of 0%), which was significantly lower than the expected mean overall score of 56.9% ($p<0.00001$). Additionally, the expected mean overall score was lower than 70%. Since the importance of genetics in primary care is increasing, it is crucial that physicians are knowledgeable about genetic testing so that they can better serve their patients.

In the current study, several variables concerning genetics education affected overall percent score. Perhaps these variables can be explored further to find innovative ways in which both medical school and residency programs curricula can be altered to improve baseline genetic testing knowledge.

Variables Affecting Overall Score

Not every resident answered all 15 case-based scenario questions, thus scores were compared for residents who answered only the first page and residents who completed the entire survey to determine if genetics knowledge differed for those five questions. As we did find a significant difference between these two groups of residents, we feel that the residents who stopped the survey early did so because 1) they felt the questions were too hard or 2) they had a lack of confidence in their ability and/or knowledge. Indeed, we found that the mean score on the first five questions for those residents who stopped after the first page was 24.4%, while the mean score on those same questions was 46.8% for those residents who finished all three pages ($p=0.024$). Furthermore, the overall observed correct score of 43.0% (regardless of number pages completed) might be an overestimate of this population's genetics knowledge if the reason that some residents stopped early was in fact due to lack of knowledge.

The mean overall correct score was significantly lower for family practice residents. We speculate that a lack of genetics training is at least one reason explaining why these residents scored lower compared to residents from other programs. Family medicine residency curricula include more varied rotations (e.g. internal medicine, obstetrician/gynecology, surgery and sports medicine, etc.) and less time in pediatrics, [41], leaving less time for more specialized rotations such as genetics. In UT's family practice residency program, a genetics rotation is not a requirement. The only genetics experience these residents receive is if they work with a genetic counselor and/or geneticist during their pediatric/neonatology rotation [55]. Thus, integrating more genetics training into these rotations is probably the best option for family medicine residency programs, as it is likely that they will encounter a baby with an underlying genetic condition while in their one short nursery rotation.

The mean overall correct score was significantly lower for residents who attended medical school abroad compared to those who graduated from medical schools in the United States. Nearly 86% of our population of foreign medical school graduates (12 of 15) was comprised of family practice residents. Given that family practice residents scored lowest overall, we contend that the low scores among foreign medical school graduates is more reflective of their residency training than of where they attended medical school. Indeed, once residency specialty was accounted for, multivariate analysis showed that location of medical school training was no longer a significant predictor of overall score.

The last variable that affected mean overall correct score was nature of the genetics rotation in medical school. Residents who elected to complete a genetics rotation in medical school scored significantly higher than those who did not undertake a genetics rotation. This is logical considering that residents who elected to complete such a rotation in their undergraduate medical education were probably interested in genetics and motivated to retain the information they learned. It should be noted that the question asking residents if their medical school required a genetics rotation caused confusion, as no medical schools in the United States are known to require its students to rotate through genetics. The misunderstanding of this question is further

evidenced by the fact that 4 residents who reported they attended medical school at UT indicated they were required to complete a genetics rotation while in medical school, when it is known that no such requisite exists at UT. Additional limitations of using a non-validated questionnaire for the study will be addressed later on.

There were several variables that did not affect overall score. Of note, residents who reported that they seek out genetic information did not score higher than those who reported that they do not seek out such information. This finding is counterintuitive one would expect that individuals who seek out genetic information would perform better than those who do not because they are interested in the subject matter, motivated to learn, and may retain the information.

Although residency year did not significantly affect the mean overall correct score, a trend was observed that residents at the end of their training scored higher than those in the beginning of their training. This pattern is to be expected, as residents in later years of residency have more overall experience than those in their earlier years. First-year residents had completed 5 – 8 months of residency by the time the survey was administered. The majority of their genetics knowledge would have largely been from their undergraduate medical education. In contrast, physicians in later years of residency may have had medical school genetics education in addition to specific genetics training in their residency programs, as well as years of genetics exposure through experience. At UT, a two-week genetics rotation is now required for all categorical pediatric residents [56]. Pediatric Neurology residents at UT also complete this two-week genetics rotation since their residency program consists of the first two years of categorical pediatrics followed by additional requirements in child neurology [57]. Internal Medicine/Pediatrics residents at UT must now also complete a one-month genetics rotation in their fourth year [58], but the family practice residency program does require any genetics at all [59]. At BCM, genetics is not a required rotation for any specialty; it is integrated into residents' curricula through a noon conference series and direct patient care [60].

When the individual scenarios were analyzed, we found certain topics that would benefit from additional instruction in both medical school and residency program curricula. These topics include: 1. Clarification of the appropriate use of CMA in a genetics work-up, 2. Clarification of the role of karyotype in genetic diagnosis, and 3. Clinical actions in the event of a positive newborn screen. Each will be discussed separately.

Appropriate Use of CMA in a Genetics Work-Up

Since chromosomal microarray analysis (CMA) is a relatively new genetic testing technology, it was given as an answer choice for 13 of the 15 questions in the survey but was the correct answer for only one question: scenario 8 (multiple congenital anomalies). It is encouraging that the majority of responders correctly answered this question. However, there were several scenarios in which residents inappropriately selected CMA as the answer choice. For the survey, there were two ways a CMA could be inappropriate for use in a clinical diagnosis. The first involved the use of CMA to detect single-gene disorders (e.g. Fragile X, Cystic fibrosis, Noonan, and achondroplasia). The second involved ordering a CMA in conjunction with another test when both tests give the same or similar information (i.e. redundant genetic testing).

It is evident from scenario 2 (Fragile X) that residents do not understand that there are some genetic conditions CMA cannot detect. Participants were given both the suspected diagnosis as well as the type of causative mutation (trinucleotide repeat). However, the majority of respondents (65.2%) chose an answer choice including CMA. Even if residents did not specifically know the meaning of answer choice E, 'Order Fragile X DNA testing,' four of the five answer choices could have been eliminated as possibilities had they realized CMA cannot detect trinucleotide repeats. Additionally, when this question was analyzed using current genetic testing prices, residents spent an average of $2,000 more than was actually necessary to make the correct diagnosis. Perhaps genetics education for physicians should make it a priority to focus on the different types of mutations that cause genetic disease and the testing methodologies designed to detect them. Grouping genetic conditions by etiology (i.e. conditions

caused by chromosome aberrations, conditions caused by single genes) would be a helpful addition to medical school and pediatric-focused residency program curricula. If no effort is made to correct the deficit of knowledge shown by this survey, health care dollars will continue to be unnecessarily used.

Similarly, scenario 14 asked residents to order testing helpful in the diagnosis of achondroplasia. Again, the suspected diagnosis was given for the question although the type of mutation was not. Nearly one-fourth (22%) of the responders incorrectly chose CMA, a testing modality that does not detect the two point mutations in *FGFR3* responsible for achondroplasia in 99% of affected individuals. More importantly, achondroplasia remains a clinical diagnosis and molecular testing is not usually indicated [61]. Molecular testing was not given as an option, and it would have been interesting to see how often it was chosen if it had been an answer choice.

The Role of Karyotype in Genetic Diagnosis

The clinical scenarios involving Down syndrome and Turner syndrome best illustrate that residents were not familiar with the correct role of karyotype in genetic diagnosis. Chromosome analysis via a routine karyotype is the only genetic test necessary to give a patient a diagnosis of Down syndrome or Turner syndrome. In addition to a diagnosis, accurate information on both etiology and recurrence risk are also obtained via karyotype. Almost 10% of residents chose CMA as the correct answer to scenario 3 (Down syndrome), an observation possibly attributed to the once-common practice of ordering the test alongside karyotype when CMA first became clinically available.

Also in scenario three, roughly half (50.7%) of respondents chose an answer involving FISH for chromosome 21. It is possible that these were popular answer choices simply because they were the only ones that made reference to chromosome 21. Moreover, there could also be confusion since aneuploidy FISH is commonly used to diagnose chromosomal aneuploidies prenatally to facilitate timely decision-making during pregnancy. Alternatively, residents might be unaware of both the limitations of FISH for chromosome 21 and the expensive nature of the technology. FISH for

chromosome 21 can certainly identify three copies of chromosome 21 in the vast majority of cases, but it cannot differentiate between free trisomy 21 and translocation 21. The difference between free and translocation trisomy 21 is essential in giving families correct recurrence risk information. Additionally, FISH for chromosome 21 costs several hundred dollars, when the cost of a routine karyotype is all that should be expended. This extra expense is generally not justified when a non-lethal aneuploidy, such as Down syndrome, is suspected.

While it is not outside the realm of possibilities that microarray technology, or something similar, will eventually be able to differentiate between Down syndrome caused by a translocation and Down syndrome caused by free trisomy 21, currently a karyotype gives the most complete information needed in a clinical setting. Additionally, at least one major clinical genetic testing laboratory has explored array technology for the detection of sex chromosome imbalances like Turner syndrome [62], although there remain limitations to sensitivity that should be resolved before CMA is ordered in place of a karyotype.

Clinical Actions in the Event of a Positive Newborn Screen

Residents had the second lowest percent correct rate (6.9%) for the scenario involving a positive newborn screen for PKU. However, the score on the question is probably not an accurate assessment of residents' knowledge for the following reasons. In the state of Texas, for a positive first newborn screen for PKU, plasma amino acids should be ordered in conjunction with a consultation and/or referral to a metabolic specialist [63]. In addition, a second newborn screen should be drawn, if it has not already been done. The answer choice that the committee deemed correct was an immediate referral to a metabolic specialist, an answer that does not completely reflect recommended guidelines. Nearly half of all residents (47%) chose 'switch the child to a low phenylalanine diet, order plasma amino acids, and repeat the newborn screen.' While we initially chose immediate referral to a metabolic center as the correct choice, because the overall instructions for the survey state that all answers should be done in conjunction with a referral to a genetics specialist, this answer choice was redundant. If used in future surveys, this particular scenario will need to be re-worded.

It should be noted that the ACT Sheet, provided to physicians by the Texas Department of State Health Services in the event of a positive newborn screen for PKU, states that the child's diet should not be changed until the second screen comes back positive. Thus, the 68% of residents who selected one of the two answer choices that included switching their patient's diet still answered incorrectly. For our survey, residents were provided space at the end to write comments about the survey and there were no comments about the question being particularly "tricky." Respondents' comments can be found in Appendix E.

Variables Affecting Individual Questions

As stated in the results, there were several variables that significantly affected the percent correct rate for individual scenario questions. When the observed correct answer rate for a particular scenario question was affected by one or two variables, it was likely an artifact of small sample size and not due to a true difference in genetic testing knowledge. Residency specialty significantly affected observed correct rate for several questions; however, this could be explained by the fact that family practice residents performed worse overall than residents from the other three programs.

Possible Ways to Increase Genetic Testing Knowledge Among Primary Care Providers

Acknowledging that genetics is a rapidly expanding field and that appropriate testing frequently changes, strategies should be developed to increase genetics knowledge and keep practicing physicians up-to-date in standard medical practice. Restructuring undergraduate medical education in genetics like Baylor College of Medicine (BCM) has done gives students the opportunity to begin learning about genetics and medicine simultaneously as early as possible. It would be illuminating to perform a study similar to this one comparing medical residents who completed a genetics track while in medical school to those that did not. In fact, BCM has such longitudinal studies planned for the future [45]. However, it is expected that only those medical students who choose to focus on genetics during medical school will have increased knowledge.

For students who do not choose a genetics track, supplemental education is needed from another source. Several studies of physicians have suggested that current genetics instruction is too focused on rare disorders and not focused enough on common conditions like high cholesterol [48]. To increase clinical relevance of genetics, it has been advocated that medical schools teach genetics in an integrated manner and/or teach genetics in a way that is clearly applicable to a particular clinical specialty [64,65]. Our data did not support the fact that integrated teaching was better for medical school genetics instruction, as residents who had a dedicated genetics class scored higher overall than those who had genetics integrated into their curricula. It should be noted however, that our data was only on the cusp of statistical significance and perhaps with a bigger study population, there might have been a different result

Another way to increase knowledge regarding genetic testing could be to tailor clinical scenarios to particular trainees depending on their chosen specialty. For example, autosomal dominant inheritance might be best taught to a cardiologist using Marfan syndrome as an example, while achondroplasia might be most useful for orthopedic trainees. But regardless of the chosen method and examples used, genetics education must extend from instruction about natural history and inheritance patterns to appropriate baseline clinical testing for these conditions (e.g. echocardiograms for suspected Marfan syndrome and skeletal surveys for suspected achondroplasia).

Reigert-Johnson, et al. (2004) highlighted several potential areas of improvement for genetics education. A notable proposal was that residents be formally supervised by a member of a genetics department [66]. However, due to the paucity of genetics professionals in healthcare practice, it would be difficult to execute this idea [67]. Although it could be ideal, long new patient wait lists would prevent most clinical geneticists from entering into such agreements with primary care practices. An academic medical center would be better able to implement the suggestion, but even our clinical pediatric service at UT in the Texas Medical Center has found that such an agreement would be impossible given our high patient volume. Another potential solution provided by Reigert-Johnson, et al. is participation of medical geneticists in

Morbidity and Mortality (M&M) conferences, thus encouraging physicians to consider and appreciate the contribution of genetics to illness.

Addressing deficits of genetics education in medical school and residency programs still leaves the very large population of practicing physicians who are no longer in residency but need to be kept current on rapidly changing genetic testing technology. To remedy the problem, credentialing should consider endorsing genetics-focused CME opportunities.

Other potential solutions exist to encourage PCPs to work collaboratively with medical geneticists and genetic counselors. Since we have established that medical geneticists likely do not have the time required to supervise residents in practice, these healthcare professionals could choose to mentor in other ways. At UT, medical geneticists and genetic counselors regularly give grand rounds presentations about genetics and genetic testing to attending and resident physicians on a variety of topics including genetic testing and newer technology such as Non-invasive Prenatal Diagnosis (NIPD). Given that genetic counselors are specifically trained to explain complex genetic concepts to individuals with varying knowledge bases, perhaps genetic counselors can invite their pediatrician colleagues to such presentations. Such multi-disciplinary collaboration would likely increase PCP knowledge and their understanding of the role genetics plays in disease.

Building on the idea of multi-disciplinary collaboration, we propose that pediatric-focused PCPs should consult their genetic-focused colleagues more when encountering a patient who could have an underlying genetic condition. Examples might include consulting with a geneticist or genetic counselor about appropriate first-tier genetic testing to order or asking whether a child would benefit from a referral to a genetics specialist. Collaboration in hospitals or doctors' offices when genetic testing is being ordered could potentially decrease the monetary burden of genetic services on the health care system. In addition, similar to ARUP, more laboratories could use genetic counselors to assess their testing requests to decrease duplicate or redundant genetic testing. Furthermore, LBJ General Hospital in Houston, TX is piloting a genetic

screening clinic program with certified genetic counselors evaluating children and their family histories to recommend appropriate genetic testing before the child has an appointment with the medical geneticist. The idea of a pediatric genetics screening clinic has the potential to help with both over-crowded genetics clinics and with reducing unnecessary genetic testing.

Strengths and Limitations

Our study is the first to focus on the current use of Chromosomal Microarray Analysis in primary care and has provided preliminary evidence that pediatrics-focused residents are aware of the test but do not understand its appropriate use. In addition, cost analysis was incorporated into our study. This was found to be a limitation to previous studies of physician knowledge of genetics [31].

We have examined the lack of genetics knowledge among health care providers in a novel way; however we acknowledge some limitations to our study. The limitations include self-reported data, small sample size (n=81) and use of a non-validated questionnaire. As mentioned previously, it appears that the demographic question regarding a required genetics rotation in medical school caused confusion, since 10 residents indicated their medical schools required a genetics rotation. If this survey is used again in the future, this question will need to be reworded since there are no medical schools in the United States known to require such a rotation of its students. Repeating this study with greater number of residents and a validated survey tool would make the results more generalizable. Furthermore, we were not able to recruit family practice residents from BCM. If the BCM family practice residents had participated, the overall score of family practice residents may have been higher. However, it should be noted that medical school affiliation for residency programs did not significantly affect overall score for the other three specialties, so family practice residents from BCM may have performed poorly as well.

We also acknowledge that the correct answer for each case-based scenario question was determined by a small number of practicing genetics professionals. While every effort was made to ensure that our determination of the correct answer was in

line with current guidelines and recommendations, we concede that standard of care is different among institutions.

We anticipated that residents might use down time to answer the survey (i.e. answering the questions in an on-call room), so we had to enable multiple answers per computer to get the highest response rate. Additionally, although we asked residents to answer the questions from their own knowledge and not to consult any references, we cannot guarantee that they did not do so. Since residents had low genetic testing knowledge overall, we do not expect that any such collaboration would have significantly increased percent score overall.

Future Directions

A study of a larger group of residents who elected to take genetics in medical school to assess how they initially became interested in genetics could be enlightening. Such an analysis might highlight ways to increase the population of medical students who have an interest in genetics. Also, just as we have suggested that primary care physicians should collaborate more with genetics professionals, the genetics work force should make every effort to ensure that genetics resources are up-to-date. For example, 'Genetic Testing 101', an educational resource published by the National Coalition for Health Professional Education in Genetics, does not contain any information about array-CGH technology [68].

Conclusions

In conclusion, the results of the current study supported our contention that pediatrics-focused are deficient in their knowledge about first-tier genetic testing as it pertains to clinical practice. While previous studies have focused on physician recall of genetic information, this study asked residents to apply what they knew about genetics to a clinically based scenario that they might encounter in practice and determine the most appropriate first-tier genetic testing needed.

Additionally, we have provided preliminary evidence of possible excess health care spending in the course of diagnosing certain genetic conditions. This concept

should be explored further with future studies since health care costs in the United States continue to rise.

Through this study, we identified several topics for clarification with regard to genetic testing that can be used in medical education: appropriate use of CMA in the genetics work-up, the role of karyotype in genetic diagnosis, and clinical actions to be taken in the event of an abnormal newborn screen.

Several previously proposed remedies for addressing deficient health care provider genetics knowledge were also explored in the context of the results of this study. It is our hope that medical schools and residency programs continue to alter their curricula to make genetics education the most relevant it can be to clinical practice. Ultimately, strides must be taken to overcome this deficient in knowledge in first-tier genetic testing among pediatric-focused health care providers to ensure that families receive the best care possible in both a timely fashion and at a reasonable expense.

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Vita

Samantha J. Penney was born in Austin, Texas on August 9, 1987, the daughter of Steven Penney and Lesley Penney. She received her high school diploma from Round Rock High School in 2005 and then entered Southwestern University in Georgetown, Texas. After two years at Southwestern, Samantha finished her undergraduate education at The University of Texas at Austin, where she received the degree of Bachelor of Arts in Biology in May of 2009. Prior to graduate school, Samantha worked for a year as a Genetic Testing Coordinator at Baylor College of Medicine's Medical Genetics Laboratories. In the summer of 2010, Samantha became a member of the 22nd class of the University of Texas Genetic Counseling Program, where she will receive her degree in May of 2012.

Appendix A – Demographic Questions and Survey

Study Questionnaire – Demographic Information

Demographics

Please complete all of the following questions:

Age: _____

Sex: Male Female

Which residency specialty training program are you in currently?

Pediatrics
Combined Internal Medicine/Pediatrics
Pediatric Neurology
Family Practice
Other - please specify _____

In what year of residency are you currently?

1st 2nd 3rd 4th

Are you post-call today? Yes No

Undergraduate demographic questions

Did you obtain an undergraduate degree before attending medical school?

Yes No

If **yes**:

What was your undergraduate major? _____

What was your undergraduate minor? _____

If **no**, please describe your education prior to entering medical school:

_____

Do you have any post-undergraduate degrees? Yes No

If **yes,** which other degrees do you have? _____

How many genetic **courses** did you take in your **undergraduate** training?

0 1-2 3-4 5+

Medical school demographics questions

Did you attend medical school in the United States? Yes No

If **Yes:** From which medical school did you graduate? _____

In which **state** is this medical school located? _____

If **No**: From which medical school did you graduate? _____

In which **country** is this medical school located? _____

How many genetic courses did you take in **medical school?**

0 1-2 3-4 5+

Did your medical school require a Genetics rotation? Yes No

If **yes**, how many weeks was your genetics rotation? _____

If **no**, did you elect to complete a genetics rotation? Yes No

How many weeks was this elective genetics rotation? _____

Do you have children? Yes No

If **yes**, how many? _____

How many of your children are under the age of 5? _____

Have any of your children or family members been diagnosed with a genetic condition?

Yes No

If **yes**, what is the genetic condition? _____

Other _____

Have you ever taken a genetics class as an elective (i.e. not required by your degree program)? Yes No

If **yes,** how many? 1 2 3 4+

Do you subscribe to any scientific journals that are genetics-focused? Yes No

If **yes**: to which genetics-focused journals do you subscribe? _____

Do you seek out genetics information (i.e. news stories, T.V./movie documentaries, etc.) Yes No

Genetic Testing Knowledge Survey

Directions: Please read each scenario and choose the **single**, best answer, looking for the **most appropriate** first tier genetic test/clinical action to consider when evaluating a patient with a potential underlying genetic condition. **This genetic test/clinical action should be in conjunction with a referral to a genetics specialist.**

1. A 39-week G2P1 female delivers a baby weighing 3,200 g and measuring 50 cm long. This baby appears male but is determined to have ambiguous genitalia with stretched penile length of about 2 cm. The gonads are not palpable. How would you proceed?
   A. Order Chromosomal Microarray Analysis (CMA)
   B. Order Chromosomal Microarray Analysis (CMA) + Karyotype
   C. Order Congenital Adrenal Hyperplasia (CAH) biochemical screen
   D. Order Congenital Adrenal Hyperplasia (CAH) biochemical screen + Karyotype
   E. Order Congenital Adrenal Hyperplasia (CAH) biochemical screen + Karyotype + Chromosomal Microarray Analysis (CMA)

2. You have been following a 6-year-old male in your clinic with a history of significant intellectual disability, autistic features, and dysmorphic features consistent with Fragile X syndrome. Fragile X syndrome, a common genetic cause of intellectual disability, is due to a trinucleotide (CGG) repeat in the *FMR1* gene on the X chromosome. How would you proceed?

   A. Order Chromosomal Microarray Analysis (CMA)
   B. Order Chromosomal Microarray Analysis (CMA) + Fragile X testing
   C. Order Chromosomal Microarray Analysis (CMA) + Fragile X testing + karyotype
   D. Order Chromosomal Microarray Analysis (CMA) + karyotype
   E. Order Fragile X testing

3. A full-term female baby is born to a G1P0 mother with Apgar scores of 9 and 10 at 1 and 5 minutes respectively. Upon examination, you note the baby has almond-shaped eyes, epicanthal folds, a flattened face, and protruding tongue. You suspect this baby girl has Down syndrome. After talking to the mother, you learn that her sister also had a child with Down syndrome. How would you proceed?

   A. Order Chromosomal Microarray Analysis (CMA)
   B. Order Fluorescence In-situ Hybridization (FISH) for chromosome 21
   C. Order a karyotype
   D. Order Chromosomal Microarray Analysis (CMA) + Fluorescence In-situ Hybridization (FISH) for chromosome 21
   E. Order Chromosomal Microarray Analysis (CMA) + Karyotype

4. You follow a 3-month-old Caucasian baby with a history of failure to thrive. At birth, the baby had meconium ileus, and has since had a history of failure to thrive. Newborn screening for immunoreactive trypsinogen (IRT) was high and a sweat test was inconclusive. You suspect Cystic Fibrosis, which is caused by mutations in *CFTR*. How would you proceed?

   A. Order *CFTR* deletion testing
   B. Order *CFTR* full sequencing to look for mutations in the gene
   C. Order *CFTR* common mutation panel to look for mutations in the gene
   D. Order Chromosomal Microarray Analysis (CMA) to look for absence or duplication of *CFTR* gene
   E. Order Chromosomal Microarray Analysis (CMA) + *CFTR* common mutation panel

5. The maternal aunt of the baby in the previous question is starting to plan her family. Due to her nephew's genetic testing and subsequent parental testing, she knows that her sister carries a deltaF508 mutation in one of her copies of the *CFTR* gene. She decides to pursue testing and discovers that she carries this mutation as well. Her husband is of Latino ancestry. What is the most appropriate testing for him as he pursues carrier screening?

   A. *CFTR* deletion testing
   B. *CFTR* full sequencing to look for mutations in the gene
   C. Targeted *CFTR* mutation testing to see if he also carries the deltaF508 mutation
   D. *CFTR* common mutation panel to look for mutations in the gene
   E. Chromosomal Microarray Analysis (CMA) to look for absence or duplication of the *CFTR* gene

6. The parents of one of your patients tell you they are concerned because their 10-month-old daughter's fingers have started trembling. You note that the baby can sit on her own but has generalized muscle weakness and absent tendon reflexes. You suspect the baby might have Spinal Muscular Atrophy (SMA), which is caused by mutations in *SMN1*. How would you proceed?

   A. Order deletion/duplication testing of *SMN1* to look for deletions & duplications
   B. Order Chromosomal microarray (CMA) to look for deletion or duplication of *SMN1*
   C. Order sequencing of all exons of *SMN1*
   D. Order sequencing of only exons 7 and 8 of *SMN1*
   E. Order targeted deletion analysis of exons 7 and 8 of *SMN1*

7. You see a 28-month-old boy as a new patient in your clinic that has developed severe hyperphagia. His mother tells you she has put locks on all cabinets containing food. His mother is very confused because when her son was a baby, he never liked to eat and even had a history of failure to thrive. His mother tells you that her son never does what she asks him to do and throws frequent temper tantrums. Upon examination, you note the child has a hypoplastic scrotum and cryptorchidism. You suspect this child might have Prader Willi syndrome, which is caused by mutations in *SNRPN*. How would you proceed?

   A. Order Chromosomal Microarray Analysis (CMA)
   B. Order FISH for the Prader Willi critical region
   C. Order methylation studies of the Prader Willi critical region
   D. Order sequencing of *SNRPN*
   E. Order testing for uniparental disomy (UPD) of Prader Willi critical region

8. You see a 3-year-old boy in your clinic as a new patient. This child has general dysmorphic features and multiple congenital anomalies that do not particularly match any one syndrome. He also has severe motor and developmental delay. How would you proceed?

   A. Order Chromosomal Microarray Analysis (CMA)
   B. Order a karyotype
   C. Order fragile X testing
   D. Order a telomere FISH panel
   E. Order a metabolic work-up (plasma amino acids, urine organic acids, acylcarnitine profile)

9. One of your adolescent patients, a 16-year-old girl, comes in with her mother for primary amennorhea. Physical exam reveals that this patient is below the 3rd percentile for height, has some hearing loss and preliminary labs reveal hypothyroidism. How would you proceed?

   A. Order Chromosomal Microarray Analysis (CMA)
   B. Order a karyotype
   C. Order a skeletal survey
   D. Order a metabolic work-up (plasma amino acids, urine organic acids, acylcarnitine profile)
   E. Order a telomere FISH panel

10. A 2-week-old baby girl comes to your clinic with one positive newborn screen for hyperphenylalaninemia suggestive of Phenylketouria (PKU). PKU is caused by mutations in the gene for phenylalanine hydroxylase (*PAH*). How would you proceed?
    A. Order plasma amino acids and serum phenylalanine hydroxylase levels
    B. Immediately refer the child to a metabolic center
    C. Order sequencing of the phenylalanine hydroxylase (*PAH)* gene and switch the child to a low phenylalanine diet.
    D. Repeat the newborn screen and switch the child to a low phenylalanine diet
    E. Switch the child to a low phenylalanine diet, order plasma amino acids, and repeat the newborn screen

11. You are referred a new male patient whose family has just moved to Houston from out-of-town. This patient is below the 3rd percentile in height, has a VSD, and developmental delay. He also has a broad, webbed neck, apparently low-set nipples, an unusually shaped chest, and characteristic facies (low-set, posteriorly rotated ears with fleshy helicies, epicanthal folds, and ptosis). How would you proceed?

    A. Order Chromosomal Microarray Analysis (CMA)
    B. Order a karyotype for Noonan syndrome
    C. Order a karyotype for Turner syndrome
    D. Order molecular testing for Noonan syndrome
    E. Order molecular testing for Turner syndrome

12. You see a 15-year-old male patient who has just moved here from Argentina. He is >97th percentile for height, has a high arched palate, long limbs, pectus excavatum. It is unknown whether he is shares some of these characteristics with other family members. How would you proceed?

    A. Order Chromosomal Microarray Analysis (CMA)
    B. Order an echocardiogram, ophthalmologic exam, homocysteine and methionine panel
    C. Order a metabolic workup (plasma amino acids, urine organic acids, acylcarnitine profile)
    D. Order an echocardiogram and ophthalmologic exam
    E. Order sequencing of the *RET* gene responsible for Multiple Endocrine Neoplasia type 2

13. You see a 2-week-old baby in clinic whose newborn screen results and CBC are suggestive of a hemoglobinopathy. How would you proceed?
    A. Order Chromosomal Microarray Analysis (CMA)
    B. Order full sequencing of the *FVIII* and *FIX* genes responsible for Hemophilia types A and B
    C. Order full sequencing of the *HBB* gene responsible for sickle cell disease
    D. Order a hemoglobin electrophoresis if not already done
    E. Order sickledex analysis if not already done

14. You see a 10-month-old child for his well-child exam and you notice that he has fallen off the growth curve. On physical exam, he has rhizomelic (proximal) shortening of the limbs, frontal bossing and midface hypoplasia. You believe this child most likely has achondroplasia. How would you proceed?

    A. Order Chromosomal Microarray Analysis (CMA)
    B. Order a metabolic workup (plasma amino acids, urine organic acids, acylcarnitine profile)
    C. Order serum calcium levels
    D. Order a skeletal survey
    E. Order vitamin D studies

15. A 4-year-old female new to your clinic presents with 20 café au lait (coffee colored) macules greater than or equal to 5 mm in diameter, most commonly on the trunk and least commonly on the head and neck. You notice she also has freckling under her arms, a speech impediment, is <5th percentile for height and >95th percentile for FOC. You suspect this child has neurofibromatosis. How would you proceed?

    A. Diagnose neurofibromatosis based on clinical criteria
    B. Diagnose neurofibromatosis after molecular testing comes back positive
    C. Diagnose neurofibromatosis after skin biopsy studies come back positive
    D. Order a Chromosomal Microarray Analysis (CMA)
    E. Order an echocardiogram

Appendix B – Cover Letter/Consent Form

Dear participants,

The purpose of this survey is to assess residents' baseline knowledge regarding diagnostic strategies for genetic diseases. This study is composed of 15 multiple choice, scenario-based questions which we hope will allow greater understanding of current knowledge regarding this topic. Space is available for additional comments should you find this necessary.

Please complete the demographic data and then answer the short survey. Do not write any information on the survey which would identify you personally. Please complete the survey from your own knowledge offhand and please do not use any outside resources, including other healthcare professionals.

Completion of this anonymous survey is voluntary and for research purposes only. No information will be associated with any individual participant. Your answers will not be available to any of your instructors or to your program director and will in no way be used to evaluate you in your program. Data will be analyzed in aggregate and presented as part of a thesis project at the University of Texas Graduate School of Biomedical Sciences at Houston. By completing and submitting this survey, you are implying consent to have your answers used and shared among collaborators for this study. There is no financial compensation for taking this survey.

After the completion of my project, the answers to my questions will be made available to you, should you be interested. If you have questions or concerns, please contact Samantha Penney or Sarah Noblin, MS, CGC at 713-566-5938.

Thank you again for your participation.

Samantha Penney
UT Genetic Counseling Student
The University of Texas Graduate School of Biomedical Sciences at Houston
Principle Investigator

Sarah J. Noblin, MS, CGC
Assistant Director, UT Genetic Counseling Program
The University of Texas Health Science Center at Houston
Department of Pediatrics
Committee Chair

Appendix C – Test Pricing

Test	Price ($)
CMA	1780
Karyotype	740
FISH for Chromosome 21	630
Fragile X trinucleotide repeat analysis	390
CAH screen	121.75
Telomere FISH	1030
Plasma Amino Acids	235
Urine Organic Acids	253
Acylcarnitine Profile	311
Molecular testing for Noonan (PTPN11 sequencing)	1750
Echocardiogram (does not include technical fees or interpretation)	1700
Ophthalmologic Exam	205
RET sequencing	1380

Appendix D – Variables Tested for Significance

Gender
Residency specialty
Residency year
Med school affiliation
Post-call
Undergrad major
Undergrad minor
Any genetics in undergrad (Y/N)
Med school in U.S. (Y/N)
Number of children
Children under 5 years
Family history of genetic condition (Y/N)
Set-up of genetics classes in medical school (dedicated/integrated/not addressed)
Required genetics rotation med school (Y/N)
Year genetics was taken in med school
Nature of genetics rotation (none/required/elective)
Length of elective genetics rotation
Number of genetics classes in college undergraduate

Appendix E – Free Response Comments About the Survey

"too long"

"I'd be fascinated to get feedback on how I did."

"I would like to know the answers when the study is done. That would be helpful and informative for my practice. Thanks! Great survey!"

I would love to be able to get feedback on my responses."

"Too long"

"It would be nice to have the answers to these questions!"

"I probably got most of these wrong but I don't believe in pan-CMAing people"