Communicating Genetic Concepts to Primary Care Providers: ACMG ACT Sheets as "Just in Time" Resource

by

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Communicating Genetic Concepts to Primary Care Providers Using Online Resources

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Abstract

Introduction: As genetics become increasingly incorporated into healthcare, the role of primary care providers (PCPs) in diagnosing and caring for people with genetic conditions will continue to grow. However, many PCPs do not feel they have adequate resources to be successful in this role. This project looked at usage of the ACTion (ACT) Sheets, a "just-in-time" reference resource made by the American College of Medical Genetics (ACMG) in collaboration with the National Coordinating Center for Regional Genetics Networks (NCC). ACT Sheets provide a one-page summary of over 80 genetic conditions. These fact sheets include information relevant to PCPs such as differential diagnosis, next steps, potential referrals, and available management options. By making this information available to PCPs, development and marketing of the ACT Sheets fall under the third essential public health service – Inform, Educate, Empower.

Methods: This project analyzed website usage statistics from the ACMG webpage where the ACT Sheets are posted. Access information by state was then compared to PCP density in each state to explore whether the ACT Sheets were being used as expected. Overall usage was compared to the schedule of conferences where NCC staff promoted the ACT sheets to determine if this impacted actual ACT Sheet usage. Responses to a brief survey regarding frequency of use and satisfaction with the ACT Sheets were also analyzed.

Results/Conclusions: Visitors to the webpage were from all 50 states. There was a direct relationship between the state population or number of PCPs and number of visits. For impact of promotional activities at conferences, there was evidence for higher ACT Sheet usage in months where the NCC attended at least one conference. Most survey respondents were satisfied with the ACT Sheets and reported using the resources more than once a year.

Limitations: The ACMG website is a public website, so it is possible that a significant number of visitors to the ACT Sheet page and respondents to the survey were not PCPs. The website usage data was also pulled from the main page displaying the ACT Sheets, so it may not represent how often individual ACT Sheets were viewed.

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Preface

I would like to acknowledge the wonderful staff at the National Coordinating Center for the Regional Genetics Networks (NCC) who made this project possible, with particular thanks to Megan Lyon who worked with me to pull all the various web analytics used in the data analysis.

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1.0 Introduction

Initially incorporated in 1991, the American College of Medical Genetics and Genomics (ACMG) began as a way to create a national platform for healthcare providers involved in the emerging field of medical genetics to collaborate and be represented. In 2001, a cooperative agreement was made between ACMG and the Maternal and Child Health Bureau within the Health Resources and Services Administration (HRSA) branch of the federal Department of Health and Human Services. This agreement resulted in the formation of the National Coordinating Center for the Regional Genetics Networks (NCC) (American College of Medical Genetics and Genomics, n.d.-a; National Coordinating Center for the Regional Genetics Networks, n.d.-a). Together, the NCC and ACMG created ACTion (ACT) Sheets, a "just-in-time" resource to which primary care providers (PCPs) can refer when one of their patients either seems to be presenting with a genetic condition or has a genetic diagnosis already (American College of Medical Genetics and Genomics). The ACT Sheets work toward the two organizations' different but related goals. The ACMG's current goals are to "engage in coordinated efforts to improve patient care, ensure optimal reimbursement for genetic service providers, establish standards of care and laboratory policy, and educate members about advances important to their practices" (American College of Medical Genetics and Genomics, n.d.-a). The NCC's overarching goal is to "bring genetic services closer to local communities" (National Coordinating Center for the Regional Genetics Networks, n.d.-a).

More specifically, the NCC achieves its goal by supporting seven regional networks covering the United States: 1) Heartland Regional Genetics Network, 2) Midwest Regional Genetics Network, 3) Mountain States Regional Genetics Network (MSRGN), 4) New England

Regional Genetics Networks (NERGN), 5) New York Mid-Atlantic Consortium Regional Genetics Network (NYMAC), 6) Southeast Regional Genetics Network (SERN), 7) Western States Regional Genetics Network (WSRGN). The NCC's primary ways of supporting the regional networks are promoting a nation-wide infrastructure that can support an increase in genetic services usage in an equitable way, working with regional networks to create quality improvement programs, making recommendations regarding delivery and financing of genetic health services, and providing technical support (National Coordinating Center for the Regional Genetics Networks, n.d.-a). As of 2017, the NCC also works with the National Genetics Education and Family Support Center (NGEFSC) – a three-year initiative seeking to improve access to quality genetic services by building networks of partners, including people with genetic conditions and their families (National Coordinating Center for the Regional Genetics Networks, n.d.-b)

Currently, the ACT Sheets are being promoted by the National Coordinating Center for Regional Genetics Networks through their website and social media, the ACMG website, and through direct communication at conference booths. The ACT Sheets are also available on websites such as the National Library of Medicine and Up-to-Date that would be more commonly used by non-genetics professionals (American College of Medical Genetics and Genomics, 2001; UpToDate, n.d.).

It is well established that PCPs often do not have the knowledge base necessary to provide information on genetics and genetic conditions or make all the proper referrals (Bellcross et al., 2011; Cohn et al., 2015; Cragun, Scherr, Camperlengo, Vadaparampil, & Pal, 2016; Dekanek et al., 2020; Hayeems et al., 2013; Kemper, Uren, Moseley, & Clark, 2006; Moeller, White, & Shisler, 2006; Nair et al., 2017; Oyeku, Feldman, Ryan, Muret-Wagstaff, & Neufeld, 2010; Pal et al., 2013; Vickery et al., 2014). This is problematic, especially given the critical role of PCPs in

identifying patients who could benefit from genetic care (Harding et al., 2019b; Nair et al., 2017; Paneque et al., 2016). There is also a high likelihood for PCPs to interact with a patient where genetics plays a role in their health at some point in their career, due to an estimated 10-percent of people having a condition that is caused, or at least influenced, by a genetic factor (Paneque et al., 2016). This is where "just-in-time" resources about genetics, like ACT Sheets can be useful as they provide a brief overview of pertinent information for PCPs to quickly review when seeing a patient who has or may have an included genetic condition. The ACT Sheets' content will therefore ideally help PCPs make informed decisions about patient care by giving them information such as common characteristics of the genetic condition under consideration and potential referrals to make. Although there is some necessary variation between sheets, the typical ACT Sheet accomplishes this transfer of information by including sections such as Differential Diagnosis, Condition Description, Actions to Take, Diagnostic Evaluation, and Clinical Considerations, as well as including links to additional information (American College of Medical Genetics and Genomics).

As of May 2019 , there had been little, if any, analysis of whether the ACT Sheets were reaching PCPs and functioning as intended. The goal of this project is to begin to elucidate the extent to which ACT sheets are achieving this by analyzing usage data collected by the NCC. One aspect of the data is a three-question survey posted on the main page of the ACT Sheets and Algorithms page on the ACMG website. The survey was designed to pop-up upon a user entering the page. The survey data include information on users' satisfaction with the ACT Sheets. Survey responses were collected between August 2018 and May 2019. The other aspect of the data are web analytics that were pulled between August 2018 and August 2019. The web analytics data include users' geographic location – broken down by country or US state – when they access the

ACT Sheets, the number of times the pages have been visited, and the number of unique visitors versus return visitors. The number of times the pages have been visited was also broken down into visits per month and compared to a timeline of conferences attended by NCC staff where ACT sheets would have been promoted to determine the impact of such promotion on usage.

1.1 Specific Aims

- Analyze data on the usage of ACT Sheets collected via a short online survey conducted by the ACMG and web analytics from the main ACT Sheets page to:
    - Determine if marketing of the ACT Sheets impacts their usage by tracking usage trends over time in relation to various marketing efforts.
    - Assess potential barriers to ACT Sheet usage by comparing actual usage to expected usage based on regional density of healthcare providers throughout the United States.

2.0 Primary Care and Genetics: Educational Needs and Approaches

Although primary care providers (PCPs) play a vital role in identifying patients who would benefit from consideration of a genetic diagnosis, or even a formal genetics consult (Hamilton et al., 2017; Harding et al., 2019b), there is still some debate about how much they can be expected to know given their broad scope of practice. Studies have found mixed results regarding the perspectives of PCPs toward integrating genetics into their regular practice; typically, most participants are in favor of its inclusion, but there are always at least a few who are either opposed or are in favor but with clear reservations (Harding et al., 2019a; Harding et al., 2019b).

2.1 Role in Genetic Care

The World Health Organization defines primary care as a field that provides comprehensive care to people across various stages of life and disease categories (World Health Organizaton, 2019). This encompasses both prevention and treatment of a wide variety of diseases, including genetic disorders and predispositions.

Specifically regarding genetic care, a publication by Harding et al. explains the role of a PCP in genetic care from the perspective of PCPs themselves. These roles included: taking family histories and assessing risk, building care plans based on this information, and making referrals to genetics if deemed appropriate, as well as educating their patients about the ethical and psychosocial impacts of genetics – not just the medical implications (Harding et al., 2019b). A separate publication by Harding et al. defined a tiered model based on the perspectives and comfort

levels of twenty-three PCPs, as provided during interviews and focus groups. In this model, there are four stages: reassuring low-risk patients, educating patients about basics of genetic testing and ordering the applicable test, remaining involved in more complex cases, and knowing when a patient should be referred for formal genetics consult. The PCP's level of comfort and confidence in their genetic knowledge influences at which stage a PCP can fall (Harding et al., 2019a).

2.1.1 Newborn Screening

PCPs also have a role to play in newborn screening (Almannai, Marom, & Sutton, 2016; Caggana et al., 2013). Newborn screening in the United States began in 1963 after Robert Guthrie and Ada Susi published a bacterial inhibition assay to screen for phenylketonuria (PKU) using dried blood spots (Almannai et al., 2016; Caggana et al., 2013; Guthrie & Susi, 1963). Since then, numerous new screening tests have been developed and implemented to increase the early diagnosis of treatable conditions that would be severely life-altering and sometimes lethal without early interventions (Almannai et al., 2016). Screening is done by collecting a small amount of a newborn's blood through a heel prick completed within the first 24 to 48 hours of their life. This blood sample is stored on a specialized paper card, which is then sent out to a laboratory that conducts the actual newborn screening tests (Caggana et al., 2013).

The general criteria for adding conditions to newborn screening, as established by the National Academy of Sciences include: having the means to appropriately screen for each condition, cost-effectiveness, available treatments and educational resources to allow diagnosis to improve quality of life, and an overall benefit to and acceptance by the general public (Caggana et al., 2013). However, conditions are added to newborn screening on a state-by-state basis, in relation to the unique needs of each state's population, the state's financial and technological

capabilities, and state politics (Almannai et al., 2016; Caggana et al., 2013). This leads to variation in the number and types of conditions screened for between states. In the early 2000s, this was recognized to be a concern, which led to the formation of an American College of Medical Genetics (ACMG) taskforce responsible for creating a list of recommended conditions (Caggana et al., 2013). This list would develop into the Recommended Uniform Screening Panel (RUSP), which is now managed by the Health and Human Resources Administration's (HRSA's) Advisory Committee on Heritable Disorders in Newborns and Children (Almannai et al., 2016; Caggana et al., 2013). The RUSP currently consists of 35 core conditions, and 26 secondary conditions that may be found in the process of screening for the core conditions (Health Resources and Services Administration).

In the event of an abnormal result, the provider and birthing facility listed on the newborn's card will be contacted and be expected to communicate these results to the newborn's parents effectively (Almannai et al., 2016; Caggana et al., 2013). This expectation can be problematic because many of the conditions included in newborn screening are rare, and therefore many providers are not well-versed in the nuances of management of these conditions or their prognoses (Almannai et al., 2016). Providers who are not completely confident in their baseline knowledge have reported using the internet or fact sheets to refresh their memory (Finan, Nasr, Rothwell, & Tarini, 2015), suggesting that easy to access, internet-based just-in-time resources can be useful during this time (Moeller et al., 2006). In a survey of family physicians and pediatricians, a significant proportion of providers were not confident in their knowledge of newborn screening and ability to explain it to parents, with 18.5% of family physicians and 57.8% of pediatricians reporting they were up to date on newborn screening (Hayeems et al., 2013). This difference in knowledge base between pediatricians and family physicians is also reported elsewhere in the

literature. A nationwide study found pediatricians typically reporting higher levels of confidence and competence compared to family physicians in explaining newborn screening and included conditions (Kemper et al., 2006). A Massachusetts-based study that assessed PCP knowledge and confidence regarding newborn screening for hemoglobinopathies found that even when knowledge was increased by educational interventions, confidence did not increase significantly (Oyeku et al., 2010). Additional barriers, such as time constraints, have also been reported, although the majority of providers report that they are responsible for providing education on newborn screening (Hayeems et al., 2013; Kemper et al., 2006; Oyeku et al., 2010). A lack of confidence can translate into use of medical jargon instead of the patient-friendly language that becomes especially necessary for parent understanding during the potentially stressful and emotional time following a positive screen (Finan et al., 2015). Interviews of 14 PCPs in Michigan showed that some providers were unsure of the next steps following a positive newborn screen for cystic fibrosis. None of the interviewed providers had undergone any formal training in discussing these results with families and several reported struggling with how much information to provide the family prior to confirmatory testing and difficulty in answering parents' questions (Finan et al., 2015).

2.2 Need for Genetics Education

As PCPs are often the first contact for patients at risk for a genetic condition, it is important that PCPs are able to recognize telltale signs of genetic conditions (Harding et al., 2019b; Nair et al., 2017; Paneque et al., 2016). However, many PCPs lack essential skills, such as taking a family history and using it to assess whether a genetic condition seems likely (Cragun et al., 2016; Nair

et al., 2017; Scheuner et al., 2014). This results in people with genetic conditions remaining undiagnosed, and therefore untreated, which can lead to increased mortality from what would otherwise be a manageable or preventable disease (Harding et al., 2019b; Nair et al., 2017; Vickery et al., 2014). This includes HBOC, where misconceptions are prevalent about the possibility of a man to carry a pathogenic variant and have increased breast cancer risks. Among PCPs, one study showed that only 34.5-percent of respondents knew that, when assessing a patient's family history, their paternal family could be equally as important as their maternal family, and only just over half of respondents knew that males who have breast cancer are at increased risk for carrying a pathogenic variant related to HBOC (Cohn et al., 2015). Pal et al. (2013) found that although their respondents had a better understanding regarding paternal inheritance of a *BRCA1* pathogenic variant (95-percent correct), only just over half of respondents correctly answered that less than 10-percent of women with breast cancer will have a *BRCA1* or *BRCA2* pathogenic variant (Pal et al., 2013), which could lead to over-referral of lower risk patients. Another study assessed PCP's ability to correctly identify individuals at increased risk for HBOC based on family history and stratified their results by PCPs who were aware of *BRCA1* and *BRCA2* testing, but had never ordered it and PCPs who had ordered testing. They found that several PCPs (39-percent who had not ordered and 45-percent who had ordered) selected at least one low-risk family history for testing and few (15-percent who had not ordered and 19-percent who had ordered) correctly chose only the high-risk family histories (Bellcross et al., 2011).

Even within conditions on newborn screening, PCPs are not always aware of all the appropriate referrals following confirmation of a diagnosis. A Massachusetts-based study focused on PCP knowledge and practices surrounding sickle cell anemia found that 67% of participants referred patients with sickle cell disease to a specialist such as a hematologist or genetic counselor,

while only 20% referred patients with sickle cell trait even though these families could benefit from genetic counseling as well. Further, 41% of PCPs reported never discussing the implications for current and future pregnancies of previously having a child with sickle cell disease (obligate carrier status) with pregnant mothers who fall in this category (Oyeku et al., 2010). Interestingly, another study reported that a subset of PCPs (19.4% of pediatricians and 12.6% of family physicians) would refer a family to genetics following identification of a newborn carrier of cystic fibrosis, but not a newborn with sickle cell trait, even though both groups of people are carriers for a recessive condition with significant impact on health (Kemper et al., 2006). Similarly, for infants found to have hearing loss upon newborn hearing screening, the majority of PCPs (75.8%) make the necessary referral to an otolaryngologist, but very few refer families to genetics (8.9%) or ophthalmology, (0.9%) even though these are both relevant referrals due to the increased incidence of an underlying genetic factor or vision difficulties in people with congenital hearing loss. (Moeller et al., 2006). In contrast, a nationwide study found that 50% of PCPs would refer an infant diagnosed with congenital hypothyroidism to genetics, even though such a referral is not routinely recommended or necessary (Kemper et al., 2006).

It is important to note that it is not only people with rare genetic conditions who are undiagnosed. Individuals with relatively common conditions, such as familial hypercholesterolemia (FH) and hereditary breast and ovarian cancer (HBOC), are also at risk of going undiagnosed (Nair et al., 2017; Vickery et al., 2014). This is concerning due to the high number of people who could be helped if correct diagnoses were made for these conditions more often because of the changes in management that can be made to improve outcomes. In the case of FH, a diagnosis would help delay the onset of cardiac disease, which would usually occur at an abnormally young age in an untreated individual with FH, through the use of cholesterol lowering

medications (Vickery et al., 2014). In the case of HBOC, a diagnosis can lead to heightened surveillance for breast cancer in order to find and treat tumors at early stages. If the patient is not planning to have any more children, an HBOC diagnosis can also come with recommendations for a salpingo-oophorectomy, the removal of the ovaries and fallopian tubes, to help minimize the patient's risk of ovarian cancer (National Comprehensive Cancer Network, 2020), due to the current lack of effective screening for ovarian cancer (Henderson, Webber, & Sawaya, 2018). Cascade screening, which is testing first-degree relatives of individuals carrying a mutation, can also be done in both FH and HBOC to improve early diagnosis rates, and therefore improve overall health (Nair et al., 2017; Vickery et al., 2014).

There is also the issue of decreased confidence among PCPs in regard to providing genetic care. A questionnaire-based study looking at PCP knowledge and confidence in genetic testing for common chronic diseases found that only 40-percent of respondents felt knowledgeable on the genetics of common diseases. Further, only 25- and 28-percent of respondents, respectively, felt comfortable working with patients with prior genetic testing and patients who are at increased risk for a genetic condition, and only 14-percent felt comfortable discussing genetic test results with their patients (Hauser, Obeng, Fei, Ramos, & Horowitz, 2018). A questionnaire-based study of PCP knowledge and confidence regarding HBOC found that very few (less than six percent) of respondents felt completely confident in any one of several components of a discussion of HBOC: *BRCA1/2* cancer risks, inheritance pattern, result interpretation, and testing methods. None of the respondents felt completely confident discussing management changes in the event of a positive genetic result (Dekanek et al., 2020).

Continuing to use PCP knowledge of HBOC as an example, a survey-based study of family medicine physicians and obstetricians/gynecologists found that although the majority of

respondents correctly identified the definition of a variant of uncertain significance (VUS), 70-percent of respondents stated that they would recommend familial variant testing for a VUS (Dekanek et al., 2020). Similar misconceptions regarding testing for VUS in hereditary cancer predispositions have been reported elsewhere in the literature (Pal et al., 2013). This same group also found that 44-percent of respondents failed to choose the correct genetic testing for someone with a relative who has tested positive for a pathogenic variant in *BRCA1* or *BRCA2* and that only about half of respondents correctly identified the inheritance pattern of HBOC (Dekanek et al., 2020).

2.3 Approaches to Genetic Education

Overall, research has found that PCPs are aware of the limits of their knowledge on genetics and are open to learning more about relevant topics within genetics (Hamilton et al., 2017). The main approaches to educate primary care providers about genetic principles that have been discussed in the literature are continuing education courses (Houwink et al., 2015; Jackson et al., 2019; Scheuner et al., 2014; Telner et al., 2017) and just-in-time resources (Harding et al., 2019a; Harding et al., 2019b; Jackson et al., 2019; Scheuner et al., 2014). Each of these have their own strengths and weaknesses which will be discussed in the following sections. Alternative options, such as using practice tools that guide decision making in real-time have also been discussed and are usually part of a larger, multi-pronged educational approach (Scheuner et al., 2014).

2.3.1 Continuing Education

Continuing education is the most commonly discussed approach in the literature in regard to educating PCPs about current practices in genetics. Houwink et al. organized a continuing education course with an online option and an in-person option, paired with a supplementary website with continually updated information (Houwink et al., 2015). They measured the success of their program through a combination of a questionnaire requesting self-reports of genetics-related skills used in practice and a pop-up survey assessing satisfaction with the supplementary website. Through this, they found that PCPs who attended the in-person course were more likely to consider referring to a genetics specialist than PCPs who completed the online version, but both were more likely to consider referring after the course than they were before. Increased consideration of referrals did not translate into an increased number of referrals, however. This may be because more accurate referrals are being made due to the course improving knowledge of genetic risk among PCPs, which would further support success of this program. Additionally, positive feedback from their website's pop-up survey suggests that supplementing a continuing education course with a website in this manner is positively received by PCPs and improves translation of new skills into their daily practice (Houwink et al., 2015).

Telner et al. used a randomized control trial structure to assess if there is a difference in educational impact between traditional, in-person lectures and online modules for educating PCPs in genetics (Telner et al., 2017). Overall, each education group reported that they enjoyed their course and found it effective, but for different reasons. The group that attended in-person lectures appreciated the immediate feedback they received from fellow learners, instructors, and the standardized patients that were included as part of the learning process. They also commented on the fact that this structure allowed them to reinforce their new knowledge by using it first-hand

with the standardized patients. The group that completed the online modules reported that they valued the flexibility of being able to review material and complete coursework at their own pace, as well as the benefit of being able to look back at previously studied material at any point. The main aspect they reported they would like to have added was a way to discuss concepts being covered with fellow learners, such as through an online forum linked to the course (Telner et al., 2017). However, they did not find a significant difference in actual learning outcomes between the online and in-person methods. This is important because online resources are less expensive to produce and distribute and also easier for providers in remote areas to access (Telner et al., 2017), suggesting that they may be more beneficial than in-person programs.

2.3.2 "Just-in-Time Resources"

"Just-in-time" resources are resources that are intended to be reference tools for clinical decision-making support, rather than comprehensive education on a given topic. As brief internet-based fact sheets on a variety of genetic conditions that include information to guide clinical decision making, the ACMG ACTion (ACT) Sheets are one example of a "just-in-time" resource. They can be found on the ACMG website, as well as other commonly used websites such as Up-to-Date and the National Library of Medicine (American College of Medical Genetics and Genomics, 2001; UpToDate, n.d.). There is evidence that such "just-in-time" resources are well-received by PCPs, as long as they are easily accessible (Harding et al., 2019a). Many of the participants in a study conducted by Harding et al. mentioned the value of electronic resources where PCPs can access information about various genetic conditions as needed. This could include information to support clinical decision making about proper referrals. They quoted one participant talking about "websites where they can easily obtain the information and access what the next best

steps should be" (Harding et al., 2019a, p. 5). This aligns with the goal of the ACT Sheets, especially considering that each ACT Sheet contains a section detailing next steps to take, including any recommended referrals, for the given condition (American College of Medical Genetics and Genomics). The question remains, however, whether the ACT Sheets are as easily accessible as PCPs need them to be in order for the ACT Sheets to achieve this goal.

These "just-in-time" resources may also be beneficial in situations where a PCP is not as invested in taking the time to learn the details of genetic conditions. Harding et al. quoted another participant as saying, "Remembering the details is not all that important as long as you remember there is some aid. There is a piece of paper that… will give me some information about what to do with patients with genetic… issues" (Harding et al., 2019a, p. 5). Admittedly, this is an understandable viewpoint given the broad scope of what PCPs are required to manage regularly. However, from a genetic care standpoint, the concern here is whether or not having this preliminary level of understanding will be enough to recognize when a genetic condition should be considered to allow the appropriate next steps, including referrals to be made.

Harding et al. also mention a lack of up-to-date reference materials as a barrier to PCPs being involved in genetic care (Harding et al., 2019b). This is another area where "just-in-time" resources, such as the ACT Sheets, could potentially be useful, as long as they are well-maintained and regularly updated to keep up with the rapidly changing field of genetics.

2.3.2.1 ACT Sheets - Newborn Screening & More

The breadth of the ACT Sheets is rapidly expanding as new ACT Sheets are developed to cover new conditions and new categories. Initially, there were only ACT Sheets for conditions included in newborn screening (American College of Medical Genetics and Genomics). The ACT Sheets in this category are closely related to conditions listed on the Recommended Uniform

Screening Panel (RUSP). However, there are some additional conditions included in the ACT Sheets that are not on the RUSP, as well as other conditions that were recently added to the RUSP and do not have corresponding ACT Sheets yet. An example of a condition not listed on the RUSP that has an ACT Sheet is ornithine transcarbamylase (OTC) deficiency (American College of Medical Genetics and Genomics, n.d.-b). Examples of conditions that were recently added to the RUSP but did not have corresponding ACT Sheets at the time this project began are X-linked adrenoleukodystrophy (X-ALD) and spinal muscular atrophy (SMA), which were added to the RUSP in 2015 and 2018 respectively. Notably, there are ACT Sheets for five different lysosomal storage disorders, while the only lysosomal storage disorder listed on the RUSP is Pompe Disease (American College of Medical Genetics and Genomics; Health Resources and Services Administration; Health Resources and Services Administration). Refer to tables 1 and 2 for more details.

Table 1. Current ACMG newborn screening ACT Sheets

Category (American College of Medical Genetics and Genomics)	Analyte on ACT Sheet (American College of Medical Genetics and Genomics)	Conditions Included on ACT Sheet (American College of Medical Genetics and Genomics)	On RUSP? (Health Resources and Services Administration)	Rank on RUSP (Health Resources and Services Administration)	Additional Information (American College of Medical Genetics and Genomics; Health Resources and Services Administration)
Amino Acidemias	Increased Arginine	• Argininemia	Yes	Secondary	
	Increased Citrulline	• Citrullinemia I • Arginosuccinic Acidemia • Citrullinemia II (citrin deficiency) • Pyruvate carboxylase deficiency	Yes Yes Yes No	Primary Primary Secondary	
	Decreased Citrulline	• N-acetylglutamate synthetase (NAGS) deficiency • Carbamoylphosphate synthetase (CPS) deficiency • Ornithine transcarbamoylase (OTC) deficiency	No No No		

Table 1. Current ACMG Newborn Screening ACT Sheets

	Increased Methionine	• Classical homocystinuria (cystathionine ß-synthase [CBS] deficiency) • Hypermethioninemia due to methionine adenosyltransferase I/III (MAT I/III) deficiency • Glycine n-methyltransferase (GNMT) deficiency • Adenosylhomocysteine hydrolase deficiency	Yes Yes No No	Primary Secondary	RUSP lists hypermeth-ioninemia by itself, not in conjunction with MAT I/III
	Increased Leucine	• Maple syrup urine disease (MSUD)	Yes	Primary	

Table 1. Current ACMG Newborn Screening ACT Sheets

	Increased Phenylalanine	• Phenylketonuria (PKU) • Non-PKU mild hyperphenylalaninemia • Pterin defects	Yes No No	Primary	RUSP lists benign hyperphenyl-alaninemia which is a mild form a PKU, as a secondary condition. This is different from non-PKU mild hyperphenyl-alaninemia RUSP lists biopterin defects in cofactor biosynthesis and regeneration, in place of pterin defects
	Increased Tyrosine	• Tyrosinemia I (hepatorenal) • Tyrosinemia II (oculocutaneous) • Tyrosinemia III	Yes Yes Yes	Primary Secondary Secondary	

Table 1. Current ACMG Newborn Screening ACT Sheets

Endocrine Disorders	Elevated TSH	• Primary congenital hypothyroidism	Yes	Primary	
	Low T4 +/- Elevated TSH	• Primary and secondary congenital hypothyroidism • Thyroxine binding globulin (TBG) deficiency	No No		
	Elevated 17-hydroxy-progesterone (17-OHP)	• Congenital adrenal hyperplasia (CAH)	Yes	Primary	
Fatty Acid Oxidation Disorders	Decreased C0 and other acylcarnitines	• Carnitine uptake defect (CUD)	Yes	Primary	
	Elevated C0/C16+C18	• Carnitine palmitoyl transferase I deficiency (CPT1)	Yes	Secondary	
	Elevated C16 and/or C18:1	• Carnitine palmitoyltransferase (CPT2) deficiency • Carnitine/acylcarnitine translocase (CACT) deficiency	Yes Yes	Secondary Secondary	
	Elevated C4 and C5 +/- other acylcarnitines	• Glutaric aciduria type 2 (GA2) • Ethlymalonic encephalopathy (EE)	Yes No	Secondary	

Table 1. Current ACMG Newborn Screening ACT Sheets

	Elevated C16-OH +/- other long chain acylcarnitines	• Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency • Trifunctional protein (TFP) deficiency	Yes Yes	Primary Primary	
	Elevated C8 with lesser elevations of C10	• Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	Yes	Primary	
	Elevated C4-OH	• Medium/short-chain hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency	Yes	Secondary	
	Elevated C4	• Short-chain acyl CoA dehydrogenase (SCAD) deficiency • Isobutyryl-CoA dehydrogenase (IBDH) deficiency • Ethylmalonic encephalopathy (EE)	Yes Yes No	Secondary Secondary	
	Elevated C14:1 +/- other long-chain acylcarnitines	• Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	Yes	Primary	

Table 1. Current ACMG Newborn Screening ACT Sheets

Galactosemias	Increased total galactose with normal GALT (Primary or Secondary Hyper-galactosemia)	• Galactokinase (GALK) deficiency • UDP-galactose-4 epimerase deficiency	Yes Yes	Secondary Secondary	
	Absent/ Reduced GALT	• Galactosemia (galactose-1-phosphate uridyltransferase [GALT] deficiency)	Yes	Primary	
Genetic Disorders	Absent/ reduced biotinidase activity	• Biotinidase deficiency	Yes	Primary	Present on another ACT Sheet (Elevated C5-OH Acylcarnitine, Organic Acidemias)
	Hypoxemia	• Critical congenital heart disease (CCHD)	Yes	Primary	
	Elevated IRT +/- DNA	• Cystic fibrosis (CF)	Yes	Primary	
	Congenital Hearing Loss >30db	• Congenital Hearing Loss	Yes	Primary	

Table 1. Current ACMG Newborn Screening ACT Sheets

Hemoglobin Disorders	Hemoglobin FS (Sickle Cell Anemia)	• Homozygous sickle cell disease (HbSS) • Sickle beta-zero thalassemia (HbSβ^0 Disease) • Sickle hereditary persistence of fetal hemoglobin (Hb S-HPFH)	Yes Yes **	Primary Primary	RUSP lists HbSβ^0 Disease as "S, Beta-Thala-ssemia," grouping it with HbSβ + Disease
	Hemoglobin FSC	• Hemoglobin SC Disease (HbSC)	Yes	Primary	
	Hemoglobin FSA	• Hemoglobin S/Beta plus Thalassemia (HbSβ + Disease)	Yes	Primary	RUSP lists this as "S, Beta-Thala-ssemia," grouping it with HbSβ^0 Disease
	Hemoglobin FAS	• Sickle Cell Carrier/Trait	**		
	Hemoglobin FAV	• Hemoglobin Variant Carrier	**		
	Hemoglobin FEA	• Hemoglobin E/Beta Plus Thalassemia (HbE/β + Disease)	**		

**Indicates that the condition is grouped by the RUSP under "various other hemoglobinopathies" as part of the secondary conditions

Table 1. Current ACMG Newborn Screening ACT Sheets

	Fetal Hemoglobin Only (Beta Thalassemia Major)	• Homozygous beta thalassemia (thalassemia intermedia or major) • Hereditary persistence of fetal hemoglobin (HPFH)	** **		
	Hemoglobin FA + Barts Hb	• Hemoglobin A/Barts • Alpha thalassemia carrier • Hemoglobin H disease • Alpha thalassemia major	** ** ** **		
	Hemoglobin FC	• Homozygous hemoglobin C (HbCC Disease) • Hemoglobin C/beta zero (β0) thalassemia • Hereditary persistence of fetal hemoglobin (Hb C/HPFH).	** ** **		

**Indicates that the condition is grouped by the RUSP under "various other hemoglobinopathies" as part of the secondary conditions

Table 1. Current ACMG Newborn Screening ACT Sheets

	Hemoglobin FCA	• Hemoglobin C/Beta Plus Thalassemia (HbC/β + Disease)	**		
	Hemoglobin FEA	• Hemoglobin E/Beta Plus Thalassemia (HbE/β + Disease)	**		
Immuno-deficiency Disorders	-	• Severe Combined Immunodeficiency (SCID) and Conditions Associated with T-Cell Lymphopenia	Yes	Primary	RUSP lists as "Severe Combined Immuno-deficiencies" only RUSP lists T-cell related lymphocyte deficiencies under secondary conditions
Lysosomal Storage Disorders	-	• Fabry Disease	No		
	-	• Gaucher Disease	No		
	-	• Krabbe Disease	No		
	-	• Niemann-Pick Disease Type A and B	No		
	-	• Pompe Disease (Glycogen Storage Disease Type II)	Yes	Primary	

**Indicates that the condition is grouped by the RUSP under "various other hemoglobinopathies" as part of the secondary conditions

Table 1. Current ACMG Newborn Screening ACT Sheets

Organic Acidemias	Elevated C5-OH Acylcarnitine	• 3-methylcrotonyl-CoA carboxylase (3MCC) • 3-hydroxy-3-methylglutaryl (HMG)-CoA lyase deficiency • ß-ketothiolase deficiency • Biotinidase deficiency • Holocarboxylase synthetase deficiency • 2- methyl-3-hydroxybutyric acidemia (2M3HBA) • 3-methylglutaconic aciduria (3MGA)	Np No No Yes Yes Yes Yes	 Primary Primary Secondary Secondary	Biotinidase deficiency present on another ACT Sheet (Absent/ reduced biotinidase activity, Genetic Disorders)
	Elevated C5-DC Acylcarnitine	• Glutaric aciduria (GA-1)	Yes	Primary	
	Elevated C5 Acylcarnitine	• Isovaleric acidemia (IVA) • 2-Methylbutyryl-glycinuria (2MBG) (short/branched chain acyl-CoA dehydrogenase [SBCAD] deficiency)	Yes Yes	Primary Secondary	

Table 1. Current ACMG Newborn Screening ACT Sheets

	Elevated C3-DC Acylcarnitine	• Malonyl-CoA decarboxylase deficiency (malonic aciduria)	Yes	Secondary	
	Elevated C3 Acylcarnitine	• Propionic acidemia (PA) • Methylmalonic acidemias (MMA)	Yes Yes	Primary Primary, Secondary	RUSP has two different primary entries: MMA (methyl-malonyl-CoA mutase) and MMA (Cobalamin disorders); and one secondary entry MMA with homo-cystinuria)

Table 2. Primary conditions on the RUSP without ACT Sheets

3-Methylcrotonyl-CoA Carboxylase Deficiency
3-Hydroxy-3-Methyglutaric Aciduria
Mucopolysaccharidosis Type 1
X-linked Adrenoleukodystrophy
Spinal Muscular Atrophy (due to homozygous deletion of exon 7 in SMN1)

Now that the breadth of the ACT Sheets' coverage has grown, there are ACT Sheets on the topics of carrier screening, diagnostic testing, family history considerations, transitioning care from pediatric to adult providers for individuals who have genetic conditions, and – the most recent addition – handling secondary findings. The original section on newborn screening is still by far the largest with a total of 50 ACT Sheets between its nine sub-categories, while the newer sections collectively include twenty-seven ACT Sheets. The secondary findings section, especially, is expected to grow to eventually cover the entire ACMG 59 (M. Lyon, personal communication, 2019). The ACMG 59 is a list of 59 genes for which the ACMG recommends returning results to patients in cases where a pathogenic variant happens to be found through a genetic test that was not specifically looking at these genes. The recommendations are based on the penetrance of pathogenic variants in these genes and whether there is a medical benefit, such as an available treatment, to the patient knowing they carry a pathogenic variant in one of these genes (Kalia et al., 2017). Currently, the ACT Sheets cover four out of these 59 genes (American College of Medical Genetics and Genomics; Kalia et al., 2017).

2.3.3 Combinatory Approach

The online Gen-Equip project created by Jackson et al. combined case-based continuing education modules, pre-recorded webinars, guidelines, practice tools, and links to other pertinent online resources to promote genetic knowledge in PCPs. The information covered by these online materials included various categories of genetic conditions, how to take a family history, when to make a referral, and how to talk to patients about genetics (Jackson et al., 2019). After surveying 80 people spread across multiple countries, they found that the majority of users were satisfied with the resources and information based on clarity of its presentation, its accessibility, and its relevance to primary care. However, it is important to note that this may be biased due to the fact that PCPs who used this resource would have already had a pre-existing interest in incorporating genetics into their practice. They also only had 80 respondents when there were over 7,000 people who visited the Gen-Equip website in total (Jackson et al., 2019). In addition to user satisfaction, they saw significant improvement in user knowledge based on average improvements of over 20 percent between pre- and post-test scores across all continuing education modules. They also saw improvements in user confidence and changes in practice behaviors, including being more likely to take a family history and placing more value on the patient's perspective of testing. These latter results were based on interviewing 21 people who successfully completed at least one of the continuing education modules (Jackson et al., 2019).

Instead of an online system, Scheuner et al. used a clinic-based combinatory approach that involved a series of in-person lectures, patient- and provider-facing fact sheets, links to internal and external resources within their electronic health record system, a pop-up reminder to take a family history with built-in questions to guide decision-making regarding follow-up, and a form about family history that patients could fill out while waiting for their appointments. Feedback

from providers in the clinic varied for each aspect of the approach (Scheuner et al., 2014). The pop-up reminder was the most popular, followed by the lecture series and patient-facing sheets. The least frequently used resources were the links to internal and external resources, due to providers not having enough time to access and review this content during patient appointments as intended (Scheuner et al., 2014). This is important because a similar barrier may also be present in accessing the ACT Sheets, especially if a provider does not know to consider a condition prior to meeting with the patient.

2.4 Importance to Public Health

Within public health, there are ten essential services, as defined by the CDC: "1) monitor health status to identify and solve community health problems, 2) diagnose and investigate health problems and health hazards in the community, 3) inform, educate, and empower people about health issues, 4) mobilize community partnerships and action to identify and solve health problems, 5) develop policies and plans that support individual and community health efforts, 6) enforce laws and regulations that protect health and ensure safety, 7) link people to needed personal health services and assure the provision of health care when otherwise unavailable, 8) assure competent public and personal health care workforce, 9) evaluate effectiveness, accessibility, and quality of personal and population-based health services, 10) research for new insights and innovative solutions to health problems" (Centers for Disease Control and Prevention, n.d.).

The development and marketing of the ACT Sheets fall under the third essential service– "Inform, Educate, Empower" – because of their goal of promoting a workforce of healthcare professionals who are capable of working with people who have indications or a diagnosis of a

genetic condition through just-in-time education. The ACT Sheets are also related to the seventh essential service – Link to and Provide Care – in that they provide a reference resource for primary care providers and other non-genetics professionals. The bulleted section included on the majority of ACT Sheets describing next steps these providers need to take is especially relevant to this essential service as it often includes referrals or consults that need to be made, as well as other concrete steps a provider can take in providing care to a patient with a given disease that is covered by an ACT sheet (American College of Medical Genetics and Genomics).

This alignment with the accepted ten essential public health services highlights the importance of having a sound system for educating PCPs and other non-genetics healthcare professionals about basic genetic concepts so they can make informed decisions on how to treat or refer their patients. There is an unacceptable number of people who go undiagnosed with genetic conditions, such as genetic predispositions to cancer that are addressed by some of the newer ACT sheets, who experience preventable complications later in life (Harding et al., 2019b). The risk of this happening can be greatly diminished by educating non-genetics healthcare professionals on how to recognize such situations and act accordingly or make the appropriate referrals to genetic services.

The ACT Sheets are one small part of a much larger system that needs to be in place in order for more people to be aware of their potentially actionable genetic diagnoses. However, looking at what has worked for resources like the ACT Sheets in the past could inform future efforts to communicate genetic information to non-genetics healthcare professionals.

This study in particular used a three-question anonymous survey completed by visitors to the page within the ACMG website that contains ACT Sheets, as well as web-analytics data for this page. The web-analytics were used to evaluate the number of people accessing the ACT Sheets

in each state, compared against the number of people who could be accessing them (the number of PCPs in each state and each state's overall population), as well as to compare peaks in usage over time against conferences where individuals from the NCC would have promoted the ACT Sheets to conference attendees. The three-question survey was used to assess how frequently visitors use the ACT Sheets as well as their satisfaction with the ACT Sheets, including their ability to provide desired information in an easy-to-access way, and allowed respondents space to provide general feedback on the ACT Sheets.

3.0 Methods

3.1 Institutional Review Board

This project was determined to not be human subjects research by a representative of the University of Pittsburgh Institutional Review Board (communication in Appendix A).

3.2 Data Set

Data for this project was provided by the National Coordinating Center for Regional Genetics Networks (NCC). It includes data from a brief survey as well as web analytics.

3.2.1 Survey

The survey consisted of 3 questions, as outlined in Table 3. There were two multiple choice questions and one open-ended question, the latter of which allowed respondents the opportunity to share their thoughts and suggestions. These questions were intended to measure general usage and satisfaction with the ACT Sheets and Algorithms.

Table 3. Questions included in pop-up survey

Question	Response Options
How easy was it to find the ACMG ACT Sheet and/or Algorithm you were seeking?	Very easy, Easy, Neutral, Difficult, Very difficult
How often (on average) do you access the ACMG ACT Sheets and Algorithms?	Once a week, Once a month, Once a year, Less than once a year
Any other feedback you would like to provide on how the ACMG ACT Sheets and Algorithms are displayed on the ACMG website?	Open-ended

Survey responses were collected from August 2018 to May 2019. The survey was administered via a pop-up window that appeared upon viewing the ACMG's main page where all of the ACT Sheets and Algorithms are listed. Visitors to the site had the option of closing out of the survey without answering the questions if they did not want to answer the survey. The survey would pop-up every visit until it was completed, each time with the option of being closed without responding. Once the survey was answered, the survey would no longer pop-up for an individual using the same computer, limiting the same visitors from responding multiple times.

3.2.2 Web Analytics

Web-analytics were pulled from August 2018 to August 2019 for the main page where all of the ACT Sheets and Algorithms are listed. The web-analytics included the number of overall visits to the site, the number of unique visitors, the number of returning visitors, the number of overall page views (the number of times a visitor opened one or more of the ACT Sheets and/or

Algorithms), the bounce rate (the rate of people leaving a page immediately after entering it), and the geographic location of visitors (broken down by state to include the District of Columbia). The total number of visits per month was also pulled for this timeframe and the schedule of conferences attended by NCC staff obtained in order to compare trends in ACT Sheet usage over time against the timing of promotional activities.

3.2.3 Demographics

The target population for this project was PCPs, because this is the population for which the ACT Sheets are designed. It is likely that the majority of ACT Sheet users and survey respondents are at least medical professionals, even if they are not PCPs, based on such providers being the target audience for the ACMG website where the ACT Sheets and survey were posted, as well as other websites that link to ACT Sheets such as UpToDate and the National Library of Medicine (American College of Medical Genetics and Genomics, 2001; UpToDate, n.d.). This is not to say that members of the general population did not access the ACT Sheets during the project's timeframe or complete the survey, especially considering that the NCC advertises the ACT Sheets on social media. Ultimately, it is not possible to confirm who visited the website or responded to the survey because no questions were asked regarding profession.

There were no formal inclusion or exclusion criteria. Anyone who visited the website during the above-mentioned time periods were able to complete the pop-up survey and were automatically included in the web analytics.

Data on the primary care provider population for each state was obtained from the Total Active Patient Care Primary Care Physicians section of the 2019 State Physician Workforce Data Report (AAMC, 2019). This report is published biennially by the American Association of

Medical Colleges, making it the most current iteration at the time of data analysis for this project. It is intended to provide state-specific data, in addition to data from Puerto Rico and the District of Columbia, on both currently practicing physicians as well as medical students and physicians-in-training to medical program directors, physicians, and policymakers and is free to access for the general public. This data will be used as a comparison data set to the location of website visitors from the web analytics data to determine estimates for expected proportion of visits to the main ACMG ACT Sheets and Algorithms webpage occurring in each state and comparison to the actual number of visits.

3.3 Data Analysis

3.3.1 Survey

Data from all three survey questions were compiled, analyzed and used to create pie charts and bar graphs using Microsoft Excel (2019). Responses from the two multiple choice questions were counted and converted into percentages of overall responses. Thematic analysis was conducted by one individual, then reviewed by one additional person experienced in qualitative data analysis. Responses from the third, open-ended question were first broken down into general themes (Positive, Negative, Mixed, Other) based on whether the response included a suggestion for the ACT Sheets and Algorithms (a negative response) or not (a positive response). The number of responses in each general theme were counted and converted to percentages. These general themes were then further broken down into more specific categories based on the specific

suggestions made by the respondents. The number of responses in each specific theme were again counted.

3.3.2 Web Analytics – Usage by State

Data on the geographic location of visitors to the ACT Sheets and Algorithms main webpage was used to assess if the number of people accessing the ACT Sheets and Algorithms in each state reflected the distribution of primary care providers across states. This was done by creating two scatter plots using StataSE 16.0. The first scatter plot compared the number of visitors to the ACT Sheets and Algorithms main web page from each state, against the number of PCPs based in each state, for a total of 51 data points. The second scatter plot compared the number of visitors to the ACT Sheets and Algorithms main web page from each state, against the total population of each state, again, for a total of 51 points. A Spearman's correlation was also calculated for each of these comparisons to assess the degree of relationship between these variables.

Data on the number of overall and unique visits to the ACT Sheets and Algorithms main web page were used largely in basic calculations of response rates to the survey.

3.3.3 Web Analytics – Usage Trends Over Time

Usage of the ACT Sheets over time was plotted as the number of visits to the ACMG ACT Sheet website each month from August 2018 to July 2019 and aligned with the seven conferences attended by NCC staff during this time (Table 4). Qualitative assessment of the relationship between usage and promotional activities at conferences was conducted.

Table 4. Names and timing of conferences attended by NCC Staff between August 2018 and July 2019

Conference	Dates
American Society of Human Genetics (ASHG)	October 16th-20th, 2018
American Public Health Association (APHA)	November 9th-15th, 2018
National Society of Genetic Counselors (NSGC)	November 14th-17th, 2018
Association of Maternal & Child Health Programs (AMCHP)	March 9th-12th, 2019
American College of Medical Genetics and Genomics (ACMG)	April 2nd-6th, 2019
American Public Health Laboratories (APHL): Newborn Screening Symposium	April 7th-10th, 2019
National Association of County and City Health Officials (NACCHO)	July 8th-11th, 2019

4.0 Results

4.1 Survey

Out of the 8,635 unique visitors to the ACT Sheets and Algorithms main web page (data not shown), only 262 responded to the survey. This is a 3.03% overall response rate.

Question-specific response rates were as follows: 261 out of 262 (99.6%) for the first multiple choice question (Figure 1), 257 out of 262 (98.1%) for the second multiple choice question (Figure 2), and 144 out of 262 (55%) for the open-ended question (Figure 3, Figure 4).

4.1.1 Survey Responses

Forty-four percent of respondents reported that they found it "very easy" to find the ACMG ACT Sheet or Algorithm they were looking for, while 29 percent found it "easy," fifteen percent were neutral, eight percent found it "difficult" and four percent found it "very difficult" (Figure 1).

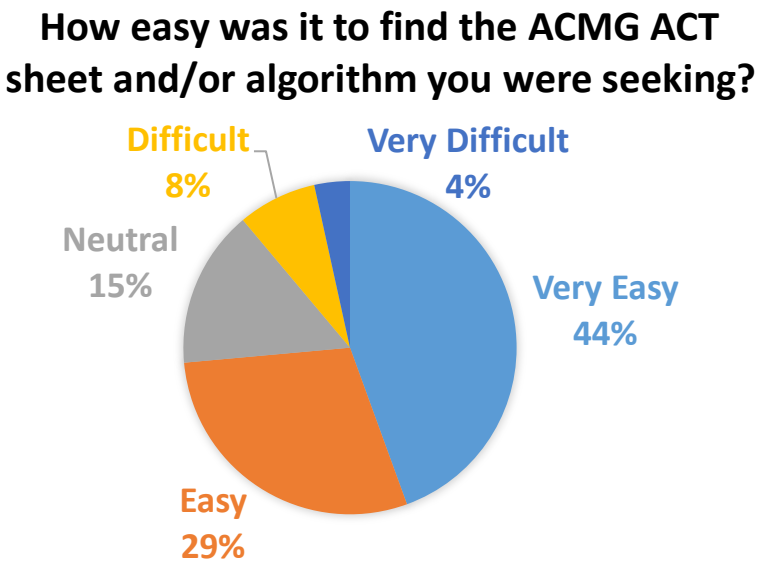

Figure 1. Responses to multiple choice question one

Eighteen percent of respondents reported that they access the ACMG ACT Sheets and/or Algorithms once a week, 38-percent reported that they access them once a month, 20-percent reported that they access them once a year, and 24 percent reported that the access them less than once a year (Figure 2).

When the responses indicating accessing these resources once a week or once a month are combined, this comes to 56 percent, or 143 of the responses. 700 visitors were flagged as return

visitors by web-analytics (data not shown). This means approximately 20-percent of return visitors completed this question.

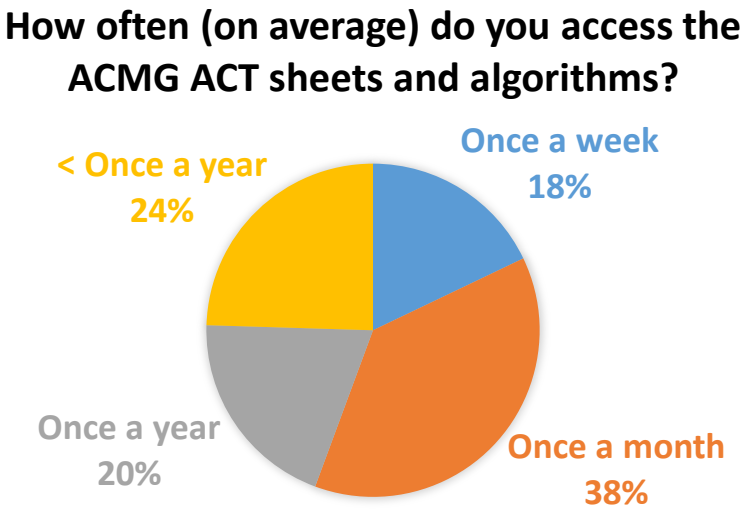

Figure 2. Responses to multiple choice question two

For the open-ended question, almost half of respondents commented with no feedback. Of the remaining 51-percent of responses, most were either positive, neutral, or negative (Figure 3). Positive responses were typically broad, often either offering thanks for the service or generally stating that the ACT Sheets were good. Negative feedback included both suggestions and direct criticisms, as well as one response that simply stated, "Yes". Neutral comments were predominantly about the survey itself or details about personal usage of the ACT Sheets, and did not reflect a positive or negative opinion toward the ACT Sheets. Mixed feedback was defined as statements that included both positive and negative connotations, such as, "Hard to get used to and find things on new website, looks nice but difficult to use." Six responses (four-percent) could not be coded because the meaning of the comment was unclear or the comment appeared to be incomplete.

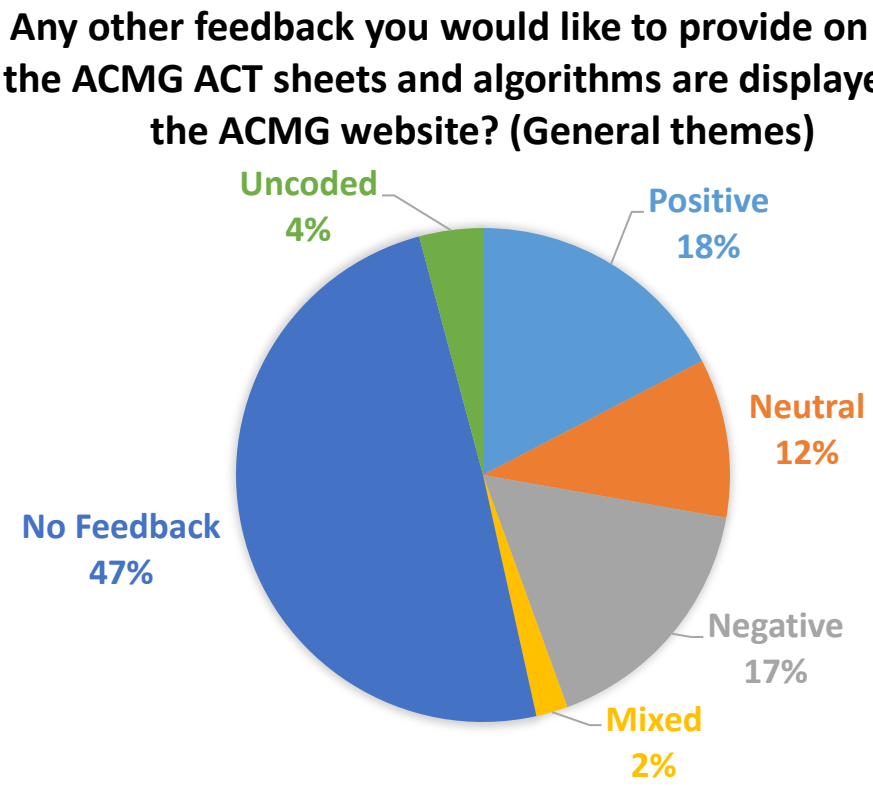

Figure 3. General themes produced from responses to the open-ended question

In focusing on coded responses containing feedback, only two responses had specific positive comments – one regarding the readability of the ACT Sheets and the other commenting on the display. Suggestions on including additional conditions, namely spinal muscular atrophy, X-linked adrenoleukodystrophy, hereditary hemochromatosis, mucopolysaccharidosis and other inborn errors of metabolism in general were made by five respondents. Alternative formats, such as small reference cards, and a need to update more regularly were also mentioned by two and three respondents, respectively. Additionally, several respondents focused on the timing of the survey – appearing immediately upon visiting the site – or on the fact that this was their first time using the site, hinting at the fact that they had not been able to review the ACT Sheets yet due to the timing of the survey. (Figure 4).

It is also important to note that one of the responses indicated that the respondent was a parent of a child who was recently diagnosed with a genetic condition who was looking for information. This confirms that not all 262 respondents, or 8,635 unique visitors to the main ACMG ACT Sheets and Algorithms webpage (data not shown), are primary care providers. The only other respondent who described their reason for accessing stated, "I am using them for education of graduate nursing students."

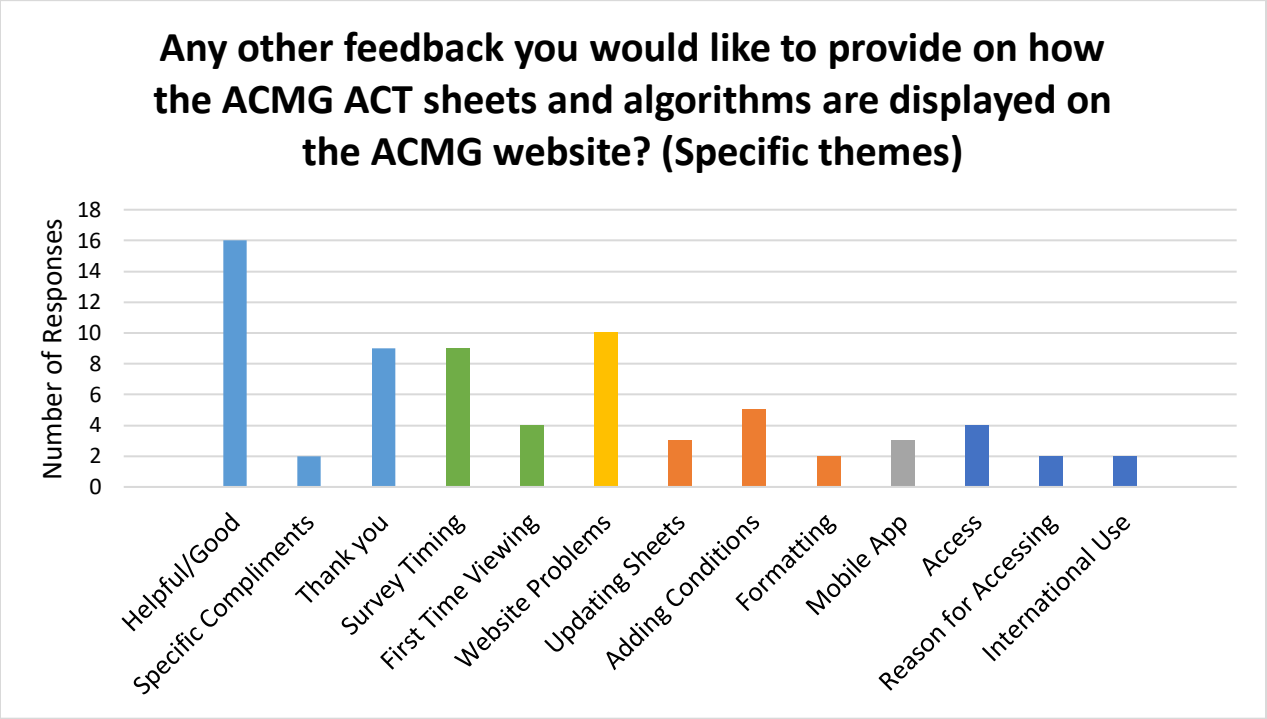

Figure 4. Specific themes produced from responses to the open-ended question

4.2 Web Analytics – Usage by State

There were similar trends between usage standardized by population size and by PCP population of each state. The District of Columbia had by far the highest usage rate, both when comparing usage to overall population size and the number of PCPs. It was followed by states such as Vermont, Utah, and West Virginia. Usage in these states are ranked differently when looking at overall population and number of PCPs, but they are all in the top three states (not including District of Columbia) in both analyses (Figure 5).

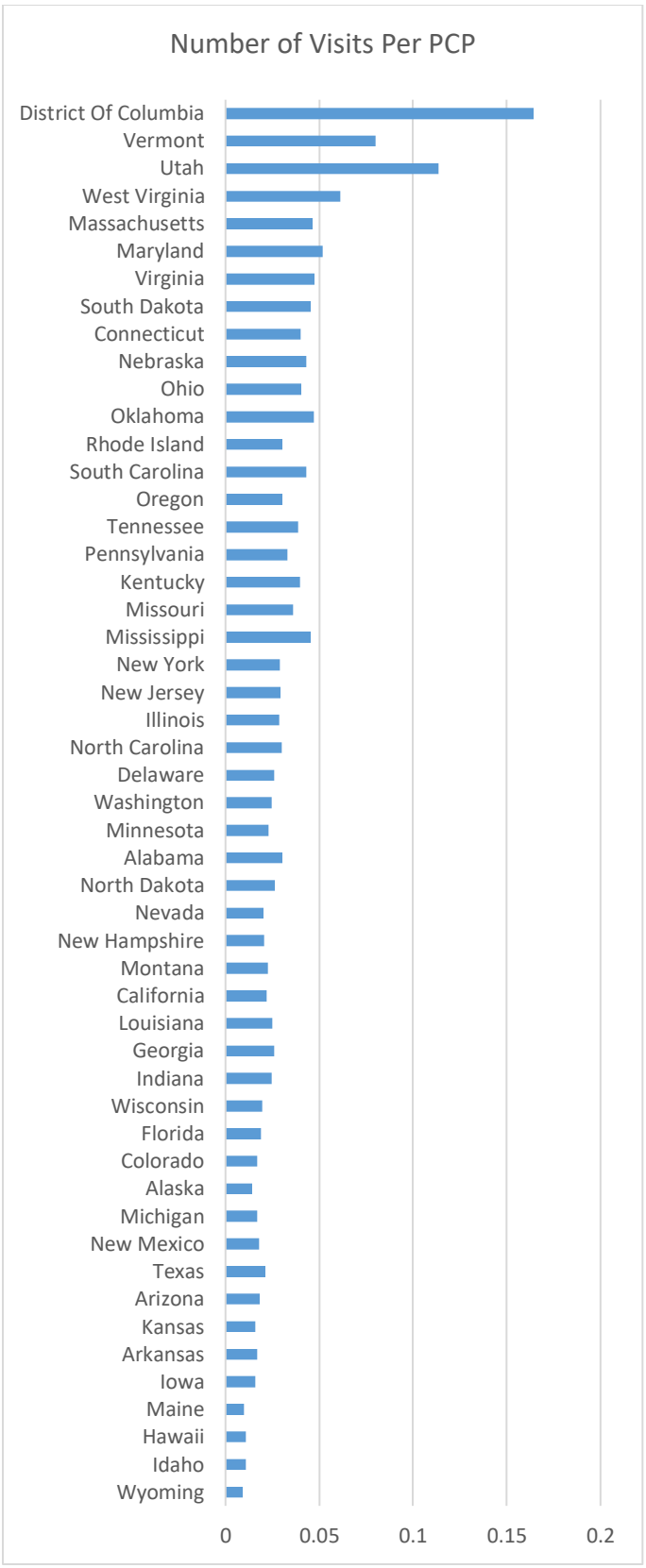

Figure 5. Number of PCPs broken down by location

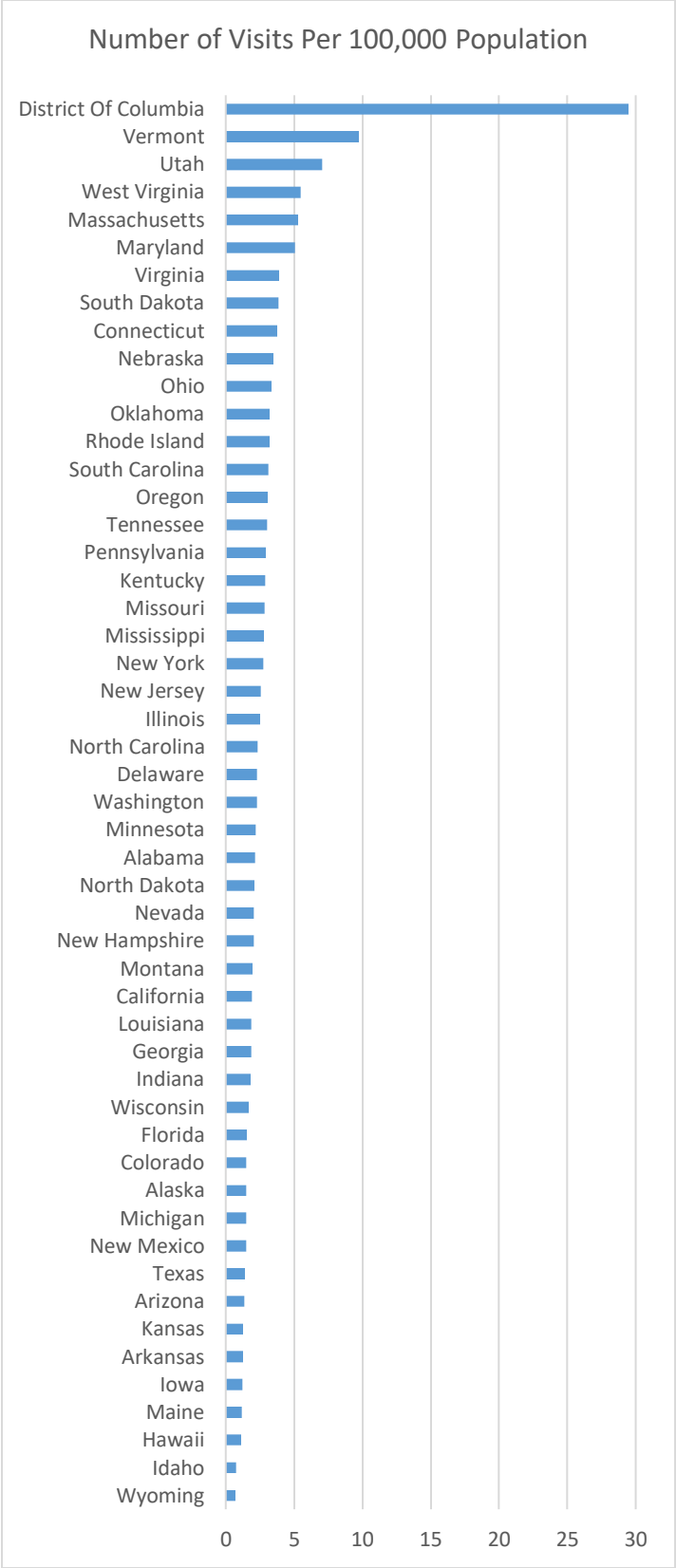

Figure 6. Rate of visits to the ACMG ACT sheets by 100,000 total state population

Figure 6 shows a direct linear relationship between the number of visitors to the ACT Sheets and Algorithms main web page from each state and the number of PCPs based in each state. Similarly, Figure 7 shows a direct linear relationship between the number of visitors to the ACT Sheets and Algorithms main web page from each state and the total population of that state. The Spearman correlation supported this relationship, with a coefficient of 0.87 (p-value: 0.0001) for the relationship between the number of visits and the number of PCPs and 0.85 (p-value: 0.0001) for the relationship between the number of visits and total population.

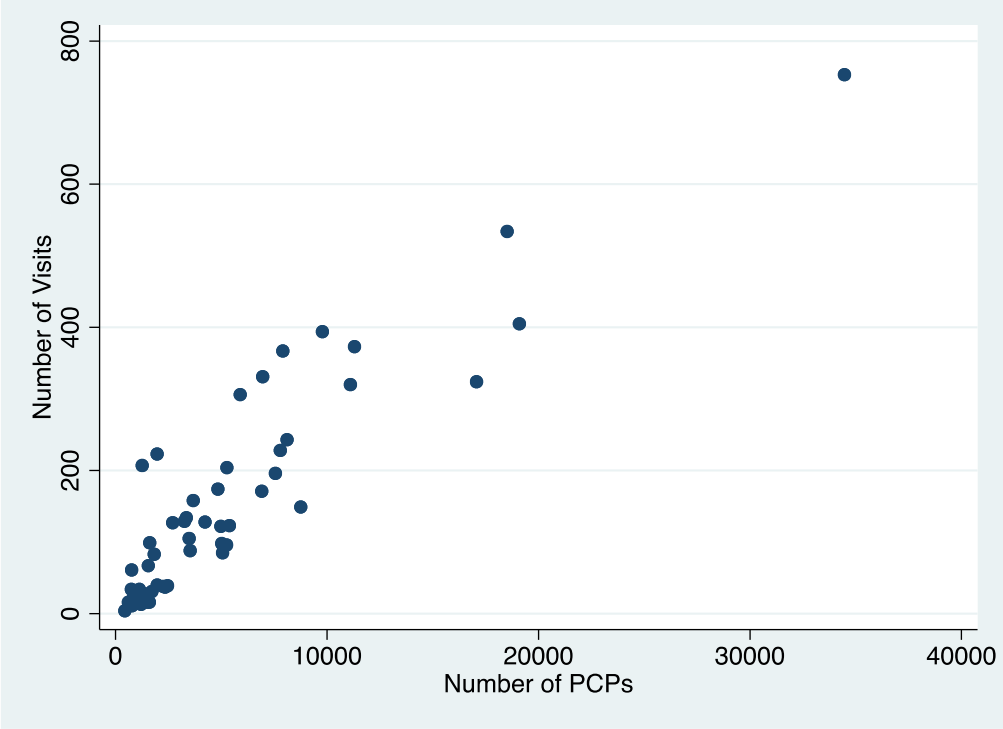

Figure 7. Plot of the number of visits from each of the 50 United States and the District of Columbia, against the number of primary care providers in that location

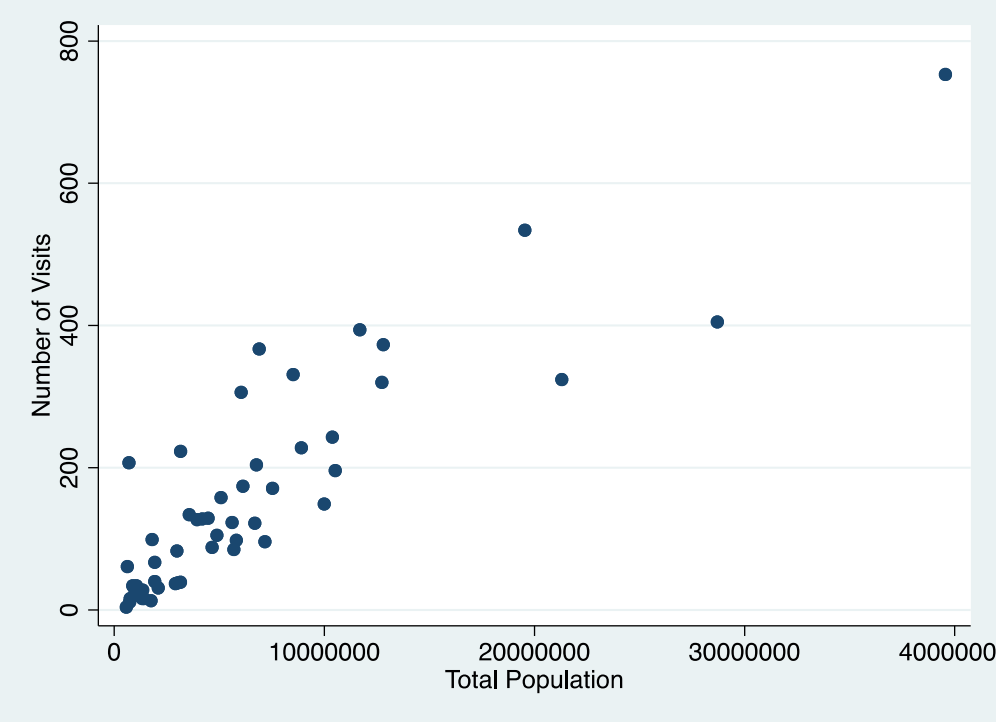

Figure 8. Plot of the number of visits from each of the 50 United States and the District of Columbia, against the the total population of that location

4.2.1 Web Analytics – Usage Over Time

Visits to the ACT Sheet website may be closely related to promotional activities at certain conferences. The months with the highest usage were October 2018, April 2019, and July 2019, all of which included at least one conference attended by NCC staff, while the months of December 2018 and June 2019 had the lowest usage (Figure 8).

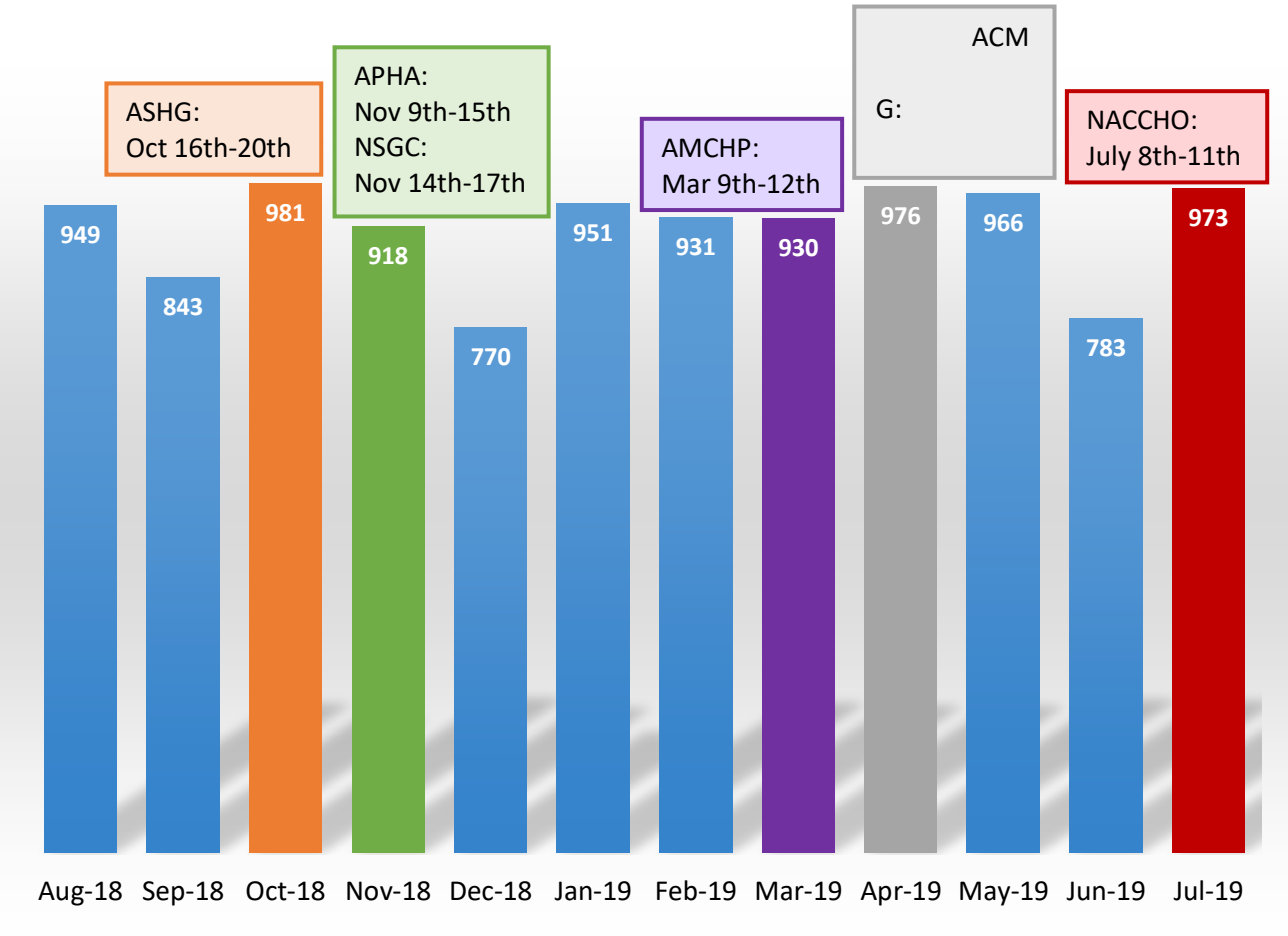

Figure 9. Total number of visits to ACMG ACT Sheets by month from August 2018 to July 2019, including conferences attended by NCC Staff during this time

5.0 Discussion

There is currently little literature available regarding usage and design of just-in-time resources like the ACMG ACT Sheets and Algorithms. The main finding of note that has been previously reported is in regard to the content of just-in-time resources. Harding et al. (2019) reported that primary care providers are less interested in learning about the underlying genetic mechanisms of a disease than they are in learning about next steps they should take, including clinical decision making and referral guidelines (Harding et al., 2019a). This is interesting because while the ACT Sheets have a complete, easy to read section on key steps to take, the molecular basis of disease is often mentioned as well, suggesting mismatched priorities between genetics professionals and PCPs. This is also relevant in the context of one of the responses to the open-ended survey question, suggesting ordering the ACT Sheets' content as a "summary [first] and then breakdown by types of disorders." Although it can be argued that having some additional information – in this case, the molecular basis of the disease – could provide the benefit of making this more detailed information readily available to providers who are interested, it seems that PCPs are not likely to need this information for their day-to-day practice. This means that adding this kind of detail may take away from the main goal of the ACT Sheets, which is to provide an easy to follow, to the point just-in-time resource for PCPs in order to help them care for patients who have or are suspected of having a genetic condition. Overall, it is likely that the formatting and content of the ACT Sheets may need to be re-evaluated with the preferences of the target audience (PCPs) in mind.

There is also the potential barrier of ease of use, making it important to determine whether the ACT Sheets are as easy to use as intended. Harding et al. (2019) reported that primary care

providers were generally open to using just-in-time resources, as long as they were easy to access (Harding et al., 2019b). In contrast, Scheuner, et al. (2014) found that providers were unlikely to click on links to just-in-time resources due to not having sufficient time to review them. However, it is important to note that Scheuner, et al. (2014) provided these just-in-time resources as part of a toolkit that providers used mostly during patient appointments, when time is even more limited than normal (Scheuner et al., 2014). It may be that just-in-time resources that are available at any time, like the ACT Sheets, are more feasible for use by primary care providers. This is only true though if the website is easy for users to navigate. As shown by the open-ended survey responses about difficulties navigating the ACMG website to find the ACT Sheets and responses to the survey question directly inquiring about ease of use, this is not the case for everyone who visits the ACMG website. It is also worthwhile to note that while only 7.6 percent of respondents commented on website problems in their response to the open-ended question (Figure 4), twelve percent of respondents reported finding it either “difficult” or “very difficult” to find the ACT Sheet or Algorithm they were looking for. This suggests that the problem is larger than suggested by the open-ended question responses, especially considering the large percent of survey respondents who chose not to answer the open-ended question.

Harding et al. (2019) also found that PCPs were interested in learning more about specific guidelines for making referrals and current reference resources that are available for use (Harding et al., 2019b). This is echoed by one of the open-ended responses from this project where a respondent asked, “Is there a link to this excellent resource from medical websites that "every" physician knows? (eg UpToDate)?” as this suggests that providers – even providers who have found the ACT Sheets – may not be aware that the ACT Sheets are in fact available on UpToDate as well as other commonly known sites like the National Library of Medicine. It is therefore worth

considering how to inform PCPs who may not know the ACT Sheets exist and therefore would not know to look for them on commonly used sites such as these. This may be especially true in light of only 24-percent of survey respondents stating that they use the ACT Sheets less than once a year (Figure 2) – the category that first-time ACT Sheet users would fall under. This means that the majority of people (at least 76-percent) who use the ACT Sheets are repeat visitors, raising the question of how many additional people could benefit from the ACT Sheets, but have not visited because they do not know that these resources exist.

Just-in-time resources have also been mentioned as a way to provide up-to-date information to primary care providers in an easy to access way (Harding et al, 2019). Assuming the problems with navigating the ACMG website can be overcome, there is still concern that the ACT Sheets are not meeting the expectation of being up-to-date. There were multiple open-ended responses that suggested the ACT Sheets needed further updating or review. These responses ranged from one respondent simply saying, "Needs updating." to another commenting more specifically, "Update ACT Sheets more frequently, the Alpha Thal sheet is from 10 years ago and gives a cutoff of 25% for Barts. Genereviews says 15% hemoglobin Barts should raise concerns for HbH disease." It is critical that reference resources like the ACT Sheets are current in order to provide PCPs and other providers with the correct information they need to treat and manage their patients.

Regarding marketing and corresponding usage of the ACT Sheets, it was unclear if there is a relationship between promotional activities at conferences and ACT Sheet usage. The three months that saw the highest number of visits to the ACMG ACT Sheet website – October 2018, April 2019, and July 2019 – all included at least one, if not two conferences attended by NCC staff. However, certain months that included one or more conferences saw fewer visits to the

ACMG ACT Sheet website than months that did not have any conferences. Namely, November 2018 and March 2019, during which NCC staff attended two conferences and one conference, respectively, saw fewer visits than August 2018, January 2019, February 2019, and May 2019 – all months where no conferences were attended. It is also not clear why the months of December 2018 and June 2019 had the lowest usage of all months between August 2018 and July 2019 (Figure 8). In the case of December, this decrease could be explained by the numerous holidays, potentially impacting the number of patients seen and need for the ACT Sheets, if there were not two conferences in November 2018 that should have theoretically carried usage over into December. A decrease in June may make more sense due to the impact of summer holidays and the fact that there had been over a month since the last conference attended by NCC staff.

The analysis of usage by states showed also large discrepancies between states for the level of usage, although there was a clear and direct relationship between both the number of visits and the number of PCPs in a state, as well as the number of visits and the overall state population. This poses the question of why certain states, such as Utah and West Virginia, have a higher rate of visits to the ACMG ACT Sheets compared to other states such as California. One possible reason for this is a higher number of PCPs per 100,000 people. However, this can be ruled out because of the wide range of PCP density among the places with the highest usage (DC: 179.4, VT: 121.5, UT: 62.2, WV: 89.4) and the lowest usage (WY: 76.2, ID: 68.9, HI: 104.7, ME: 119.7). Notably, the locations with the highest number of PCPs per 100,000 people are the District of Columbia, Vermont, and Maine (Appendix B), which are split between the highest and the lowest users of ACT Sheets. Another possibility could be the degree of marketing to PCPs by each of the regional genetics networks, or even by the individual states, which was not investigated by the current study.

5.1 Limitations

The low survey response rate (3.03%) calls the representativeness of the survey sample into question. The representativeness is further threatened considering the target population is primary care providers, but one respondent self-identified as a parent looking for information about a genetic disorder that their child was recently diagnosed with, and another respondent alluded to being a fellow in an unspecified area of medicine. It is therefore possible that the latter individual is a genetics fellow, which would make them a clearly not part of the target population. There is no way to identify the other 260 respondents' backgrounds or purposes for visiting the webpage, so it is possible, and in fact likely, that there were more non-primary care provider respondents.

As with the survey, the issue of not being able to identify how many of the visitors are primary care providers, calls the representativeness of the web analytics data of the target population into question. This is especially true for the geographic analysis because for the comparison to the current primary care provider workforce, it was assumed that there was an equal percent of PCPs making up the overall percentages of visits from each state. An equitable distribution of positive newborn screens was also assumed across states, even though no data was able to be found to support this assumption. This is important because if one state has a significantly higher rate of positive newborn screens than another state, it may be that primary care providers in the state with a higher rate have a reason to access the ACT Sheets and Algorithms more often.

Another key limitation is that all web-analytics were pulled for the main webpage where all of the ACT Sheets and Algorithms are listed, instead of being pulled for individual ACT Sheets. It may have been more informative to pull the data for individual ACT Sheets as this would have

shown which types of ACT Sheets are used more commonly, which would have alluded to what ACT Sheets are the most needed or useful.

5.2 Future Directions

Marketing of just-in-time resources was also only assessed from the standpoint of promotional activities at conferences. This leaves the opportunity for further research on the impact of other modes of marketing, such as social media. There is also currently little to no literature on the best design and distribution method of just-in-time resources. The survey results show that there are in fact aspects of the ACT Sheets that need to be changed, and the geographic analysis shows that there is a disconnect between where primary care providers are and where the ACT Sheets are being accessed. This warrants further research, potentially in regard to how marketing impacts this distribution once that data becomes available. It may also be helpful to analyze additional web-analytics data that were not analyzed here, such as bounce rate and number of page-specific views. Bounce rate may be especially useful to determine if visitors to the site were able to find information that is useful to them and remain on the site or page to read that information. This specific focus on bounce rates may be able to further inform why there is an unexpected geographic distribution of visitors to the main webpage for the ACMG ACT Sheets and Algorithms.

5.3 Conclusions

In summary, the ACT Sheets generally seem to be received positively by individuals who are aware of and reference them. The main areas of improvement, as suggested by respondents to the pop-up survey, are in promoting ease of access, structure, and content – including more regular updates of the content. There is also a need to improve marketing of the ACT Sheets to providers, especially in certain areas of the country. It is unclear whether marketing in the form of promotional activities at conferences is the best way to achieve this goal. Lessons could be learned regarding marketing by further investigating reasons why certain states, such as West Virginia and Utah, have such high rates of ACT Sheet usage compared to many other states.

Appendix A IRB Communication

Tuesday, March 23, 2021 at 13:23:36 Eastern Daylight Time

Subject: RE: Human Genetics MPH Essay
Date: Monday, October 28, 2019 at 11:47:13 AM Eastern Daylight Time
From: Ivanusic, Carolyn
To: Sprague, Trinity

Hi Trinity,

There are no IRB forms or IRB processes for studies that are not under IRB purview. The email documentation should suffice. You can forward it to your mentor for documentation. To sum up why no IRB review is needed:

The IRB only reviews projects that meet the definition of human subjects research. By definition, receipt and analysis of a dataset that includes no identifiers, nor any information that could enable the Pitt study team to obtain identifiers, does not meet the definition of human subjects.

Carolyn

****

Carolyn Ivanusic, MSW CIP
Research Review Specialist
University of Pittsburgh
Institutional Review Board / Human Research Protection Office
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3500 5th Avenue, Pittsburgh PA 15213
Phone: 412-383-1789
ivanusic@pitt.edu
www.hrpo.pitt.edu

Join the HRPO mailing list here.

From: Sprague, Trinity <TRS106@pitt.edu>
Sent: Monday, October 28, 2019 11:33 AM
To: Ivanusic, Carolyn <ivanusic@pitt.edu>
Subject: Re: Human Genetics MPH Essay

Hello Carolyn,

My advisor suggested completing an IRB form to get additional documentation to include with my essay stating I did not need IRB approval. However, I am having difficulty finding this on Pitt's IRB site. Do you know where I could find this?

Best,
Trinity
--
Trinity Sprague
University of Pittsburgh
MPH/MS Candidate | Public Health Genetics & Genetic Counseling
Graduate Student Research Assistant | Center for Craniofacial and Dental Genetics
trs106@pitt.edu

Appendix B Supplementary Data

Helpful/Good
No, they are great
Very helpful
It is very useful
I like the way it is
Great job!
I think is a very useful tool for genetics practice
love them
very helpful information
its nice to read, doing great. Keep it up
very good
great resource
Great tool
Great job
useful
good
with having this information on the web and expertly written states don't have to develop their own, we can just link to yours

Survey Timing
Please stop blocking my view
Its very difficult to find the sheet that I want with this pop up box in the way. Make your survey move off the page until I have completed my task.
I have not searched yet - your popup to the survey came up before I had a chance to search
Your survey occurs before I have opened the document
I just clicked on the website. I think this questionnaire pops up too soon before I have had a chance to look at the website for the first time
Survey popped up before even one sheet located -- no way forward without answering -- probably won't net you the data you seek with survey
this is the first time using and I haven't even gotten on website yet but got this survey
asking these questions before I've had a chance to search will not provide meaningful answers
yet to see

First Time Viewing (but don't mention survey)
I just logged in for the first time
I just learned about these and may access them more often now that I'm aware of them
just joined
first time here

Website problems
The new ACMG website is horrible, can't find anything
Every time I click on the ACT sheet, it prompts a page not found error
search button
hard to get used to new website and where things are
I always end up going back to google and typing ACMG ACT sheets because I don't know where to go from the ACMG home page
responsive web design would be better to present, interactive display may be added
links are not active
just having the words ACT Sheets as an option like your old page would be great!
hard to get used to and find things on new website, looks nice but difficult to use
just used to previous website design

Specific Compliments
Algorithms are clear and easy to follow
Display is good.

Updating
Need updating
how often are the sheets updated
Update act sheets more frequently, the Alpha Thal sheet is from 10 years ago and gives a cutoff of 25% for Barts. Genereviews says 15% hemoglobin Barts should raise concerns for HbH disease.

Missing Conditions
Sheets needed for all conditions on the ACHDNC panel
Please add SMA, X-ALD, MPS-1
inborn errors of metabolism
hh (hereditary hemochromatosis)
[nutrition] in the patient with inborn error of metabolism. Hepatopathy in the patient with inborn error of metabolism

Format problems
summary and then breakdown by types of disorders
Is there a quick reference card for each screening done for clinicians to have as opposed to sheets of paper

Mobile App
No, but mobile app needs updating to be compatible with newer devices
update the mobile app to facilitate use in the clinic
please fix the app if you haven't already. Its crucial for us, specially fellows

International Use
please try to open courses for overseas candidates
I am in [South America]. It is of great help to get algorithms for metabolic diseases. Please make it easy for us. Very thanks

Access
Is there a link to this excellent resource from medical websites that "every" physician knows? (eg UpToDate)?
send them or put them in a journal for family physician
it would be excellent if link was shorter (or if a shorter link would redirect to this site). It is hard to provide such a long link to others
outside sites should be able to link to the ACT Sheet

Reason for Accessing
I am using them for education of graduate nursing students
no. I'm trying to find help for my son. We've been told he has [a rare] syndrome

Uncoded
Did not understand that some tests have algorithms and some do not
BNA
I was trying to go to the page for Section D (shared methodologies) and ended up on the ACT Sheet page instead
I think to put statutes of the College in an easier way will be great
tha
later

Appendix Table 1. State-by-state data on ACT Sheet usage compared to general state population and PCP population

Location	Population	Number of Visits to ACT Sheets	Number of PCPs per 100,000 population	Number of visits per 100,000 population	Number of visits per PCP
AK	737,438	11	105.6	1.492	0.03
AL	4,887,871	105	71.2	2.148	0.014
AR	3,013,825	38	75	1.261	0.018
AZ	7,171,646	96	73.2	1.339	0.017
CA	39,557,045	73	87.1	1.904	0.022
CO	5,695,564	85	88.9	1.492	0.016
CT	3,572,665	134	93.7	3.751	0.04
DC	702,455	207	179.4	29.468	0.026
DE	967,171	22	87.2	2.275	0.164
FL	21,299,325	324	80.1	1.521	0.019
GA	10,519,475	196	71.9	1.863	0.026
HI	1,420,491	16	104.7	1.126	0.011
IA	3,156,145	39	77.9	1.236	0.011
ID	1,754,208	13	68.9	0.741	0.029

IL	12,741,080	320	87.2	2.512	0.024
IN	6,691,878	122	74.4	1.823	0.016
KS	2,911,505	37	80.5	1.271	0.016
KY	4,468,402	129	72.9	2.887	0.04
LA	4,659,978	88	75.8	1.888	0.025
MA	6,902,149	367	114.6	5.317	0.01
MD	6,042,718	306	97.6	5.064	0.052
ME	1,338,404	16	119.7	1.195	0.046
MI	9,995,915	149	87.6	1.491	0.017
MN	5,611,179	123	96	2.192	0.023
MO	6,126,452	174	79	2.84	0.045
MS	2,986,530	83	61.2	2.779	0.036
MT	1,062,305	21	88	1.977	0.022
NC	10,383,620	243	78.1	2.34	0.043
ND	760,077	16	79.6	2.105	0.021
NE	1,929,268	67	80.3	3.473	0.021
NH	1,356,458	28	99.6	2.064	0.0029
NJ	8,908,520	228	87.5	2.559	0.018
NM	2,095,428	31	82.1	1.479	0.029
NV	1,929,268	40	65	2.073	0.03

NY	19,542,209	534	94.8	2.733	0.026
OH	11,689,442	394	83.7	3.371	0.04
OK	3,943,079	127	68.5	3.221	0.047
OR	4,190,713	128	101	3.054	0.03
PA	12,807,060	373	88.2	2.912	0.033
RI	1,057,315	34	106.6	3.216	0.03
SC	5,084,127	158	72.3	3.108	0.043
SD	882,235	34	84.8	3.853	0.045
TN	6,770,010	204	77.8	3.013	0.039
TX	28,701,845	405	66.5	1.411	0.021
UT	3,161,105	223	62.2	7.054	0.113
VA	8,517,685	331	81.7	3.886	0.08
VT	626,299	61	121.5	9.739	0.048
WA	7,535,591	171	91.7	2.269	0.025
WI	5,813,568	98	86.4	1.686	0.061
WV	1,805,832	99	89.4	5.482	0.02
WY	577,737	4	76.2	0.692	0.009

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