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Applying Public Health Screening Criteria: How Does Universal Newborn Screening Compare to Universal Tumor Screening for Lynch Syndrome in Adults with Colorectal Cancer?

Deborah Cragun[1], **Rita D. DeBate**[2], and **Tuya Pal**[1]

[1]Moffitt Cancer Center, Department of Cancer Epidemiology, Tampa, FL

[2]University of South Florida, Department of Community and Family Health, Tampa, FL

Abstract

Institutions have increasingly begun to adopt universal tumor screening (UTS) programs whereby tumors from all newly diagnosed patients with colorectal cancer (CRC) are screened to identify who should be offered germline testing for Lynch syndrome (the most common cause of hereditary CRC). Given limited information about the impact of universal screening programs to detect hereditary disease in adults, we apply criteria used to evaluate public health screening programs and compares and contrasts UTS with universal newborn screening (NBS) for the purpose of examining ethical implications and anticipating potential outcomes of UTS. Both UTS and a core set of NBS conditions clearly meet most of the Wilson and Jungner screening criteria. However, many state NBS panels include additional conditions that do not meet several of these criteria, and there is currently insufficient data to confirm that UTS meets some of these criteria. Comparing UTS and NBS with regard to newer screening criteria raises additional issues that require attention for both UTS and NBS. Comparisons also highlight the importance of evaluating the implementation of genomic tests to ensure or improve their effectiveness at reducing morbidity and mortality while minimizing potential harms.

Keywords

Public Health Genomics; Lynch syndrome; Newborn Screening; Screening Criteria; Tumor screening

Introduction

Two key challenges in public health genomics include: 1) working together as part of a multi-disciplinary team to integrate programs, policies, and medical applications with proven efficacy into various societal settings; and 2) ensuring that these programs, policies, or medical applications have their intended effects on individuals and public health (Hiatt, 2010). As a precursor to meeting these challenges, the ACCE (**A**nalytical validity, **C**linical

Corresponding author: Deborah Cragun, Department of Cancer Epidemiology, Moffitt Cancer Center, MRC-CANCONT, 12902 Magnolia Drive, Tampa, FL 33612, Phone: (813) 745-4668, Fax: (813) 745-6525, deborah.cragun@moffitt.org.

Conflict of interest

Deborah Cragun, Rita DeBate, and Tuya Pal report no conflicts of interest

validity, **C**linical utility, and **E**thical implications) framework can be applied to evaluate the validity, utility, and ethical, legal, and social implications of genetic or genomic tests (Haddow & Palomaki, 2003). For example, the Evaluation of Genomics Applications for Practice and Prevention (EGAPP), a CDC sponsored Working Group, found sufficient evidence in favor of offering Lynch syndrome (LS) screening to all newly diagnosed patients with colorectal cancer (CRC) for the purpose of identifying family members at increased risk for this autosomal dominant hereditary cancer syndrome ("Recommendations from the EGAPP Working Group," 2009). Given that individuals with LS have a 40-70% lifetime risk of CRC (Barrow et al., 2008; Hampel et al., 2005; Stoffel et al., 2009; Win et al., 2012) and a 25-60% chance of endometrial cancer in females (Barrow et al., 2009; Stoffel et al., 2009; Watson et al., 2008; Win et al., 2012), identification of LS can lead to the effective prevention of future cancers among CRC patients and their at-risk family members (Heikki J Järvinen et al., 2009; H J Järvinen et al., 2000).

Since the EGAPP recommendation, the National Comprehensive Cancer Network (NCCN) has issued guidelines recommending LS tumor screening for either all CRC patients or for CRC patients diagnosed < age 70 and those diagnosed ≥ 70 who meet Bethesda criteria (NCCN Guidelines Genetic Familial High Risk Assessment: Colorectal, 2014). NCCN also recommends LS screening on tumors from patients with endometrial cancer diagnosed ≤ age 50 (NCCN Guidelines Genetic Familial High Risk Assessment: Colorectal, 2014). Recently, the Society of Gynecologic Oncology recommended that all women diagnosed with endometrial carcinoma should undergo systematic clinical screening (review of personal and family history) and/or tumor screening for LS (SGO Clinical Practice Statement: Screening for Lynch Syndrome in Endometrial Cancer, 2014).

Institutions have increasingly begun to implement universal tumor screening (UTS) whereby tumors from all newly diagnosed CRC patients and/or endometrial cancer patients are systematically screened using microsatellite instability (MSI) and/or immunohistochemical (IHC) testing to identify patients with tumor characteristics suggestive of LS; whereas other institutions have adopted routine criteria-based screening limited to a subset of these tumors (Beamer et al., 2012; Cohen, 2013). UTS for CRC is endorsed by EGAPP and it provides an opportunity to identify most of the estimated 28% to 70% of CRC patients with LS who are not identified when screening is limited to CRC patients who meet certain age, family history, or other criteria (J. M. Gudgeon, Belnap, Williams, & Williams, 2012; Morrison et al., 2011; Tranø, Sjursen, Wasmuth, Hofsli, & Vatten, 2010; van Lier et al., 2011).

Although EGAPP demonstrated the clinical validity and clinical utility of UTS for CRC, this Working Group did not recommend screening for endometrial tumors; nor did they provide recommendations regarding how screening should be performed ("Recommendations from the EGAPP Working Group," 2009). As such, laboratory and follow-up procedures are heterogeneous across institutions that have implemented tumor screening (Beamer et al., 2012; Cohen, 2013). Regardless of the chosen procedures, evidence of mismatch repair (MMR) deficiency in a tumor is not diagnostic of LS. Therefore, patients with MMR deficiency (i.e., "positive tumor screen") require genetic counseling to discuss associated implications and facilitate informed consent for germline testing of one or more of the genes that can cause LS (i.e., *MLH1, MSH2, MSH6, PMS2*, and *EPCAM)*.

Germline testing has been distinguished from genetic screening performed on tumors, in that the former involves DNA analysis from an individual's constitutional DNA (e.g., blood or saliva) to identify inherited mutations that increase risks for cancer, whereas the latter is typically used to predict cancer prognosis or treatment response (Robson, Storm, Weitzel, Wollins, & Offit, 2010). Microsatellite instability (MSI) testing and immunohistochemical (IHC) testing are performed on tumor tissue and can provide prognostic information for patients with colon cancer (Clark, Barnetson, Farrington, & Dunlop, 2004; Gologan & Sepulveda, 2005; Hong et al., 2012). Evidence also suggests that MSI and IHC can provide information about treatment response to 5-fluorouracil-based chemotherapy in patients with CRC (de la Chapelle & Hampel, 2010; Hong et al., 2012; Tejpar, Saridaki, Delorenzi, Bosman, & Roth, 2011). Additionally, MSI and IHC are screening tests that can be used to identify individuals at increased risk for having LS (Hampel et al., 2008).

UTS is among the first population-based genetic screening initiatives to be widely implemented on a clinical basis for the purpose of detecting hereditary disease in adults. Other widely implemented genetic screening programs are primarily aimed at identifying genetic conditions in fetuses and newborns or determining carrier status among healthy couples to assess genetic risks for offspring. Given limited information about the impact of universal screening programs for adults, we apply criteria used to evaluate public health screening programs and compare and contrast UTS with universal newborn screening (NBS) for the purpose of examining ethical implications and anticipating potential outcomes of UTS.

History of Newborn Screening

Similar to UTS, the purpose of NBS is to identify a subset of individuals at increased risk for serious health conditions (most of which are inherited) in order to offer confirmatory testing and prevent harm. The implementation of universal NBS illustrates how a public health approach can successfully decrease morbidity and mortality associated with hereditary diseases (Levy, 2010). Under these state-run programs, virtually every infant in the United States undergoes a heel stick to test for a variety of conditions (Ross, 2010). When first implemented in the 1960's, NBS panels only included diseases such as phenylketonuria (PKU) that without treatment are fatal or cause morbidity (e.g., intellectual disability) within the first few months or year of life (Ross, 2010). Thus mandating universal NBS was justified as it provided clear, direct, and substantial benefits to the infant while risks of harm were perceived to be minimal (Faden, Holtzman, & Chwalow, 1982). The application of tandem mass spectrometry (MS/MS) to NBS in the 1990s led to the identification of many metabolic conditions, some of which lacked standard evidence-based treatments and others of which had unknown clinical relevance (Ross, 2010). After the implementation of MS/MS technology, wide variability existed between NBS panels across the United States. Given NBS variability, the American College of Medical Genetics published a recommendation for a uniform panel of 29 core conditions for which all newborns should be screened ("Newborn screening," 2006). This panel was endorsed by the U.S. Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children; and two additional conditions have subsequently been added ("Recommended Uniform Screening Panel," n.d). Individual states

have adopted screening for most of these 31 core conditions, and screening is now much more uniform across the nation. A list of conditions on each state's screening panel is available online through Baby's First Test (http://www.babysfirsttest.org) and NewSTEPs (https://www.newsteps.org).

Ethical and practical concerns related to NBS arose at the time these programs were first implemented and issues continued to be debated as NBS expanded over the years. Substantial knowledge has been gained from decades of experience with NBS. In contrast, less is known about UTS programs given that implementation of UTS has only occurred in recent years. We use screening criteria as a basis by which to compare and contrast NBS and UTS. Additionally, ethical and practical implications of NBS are examined in order to identify or anticipate potential outcomes of UTS.

Public Health Screening criteria

In 1968, after states began adopting universal NBS, Wilson and Jungner introduced ten criteria that screening programs should meet before being introduced as a public health measure (Wilson & Jungner, 1968.). The Wilson and Jungner criteria are listed in Table 1 along with a description of how well NBS and UTS for LS meet each criterion.

As illustrated in Table 1, neither NBS nor UTS of newly diagnosed CRC patients met all ten of the Wilson and Jungner criteria prior to implementation. For example, the natural history of benign PKU variants was not understood prior to the initiation of NBS in the 1960s, resulting in serious harm to infants with benign hyperphenylalaninemia because they were placed on a diet that was too restrictive (Ross, 2006). Currently, most of the 31 core conditions endorsed by the Advisory Committee on Heritable Disorders in Newborns and Children meet Wilson and Jungner criteria. However, there are exceptions. For example, 3-MCC deficiency was included as a core NBS condition before an adequate understanding of the natural history of the condition existed. Whether 3-MCC deficiency is even an important health problem is questionable, given that many individuals with 3-MCC deficiency remained asymptomatic even without treatment and were identified only after a sibling was diagnosed via NBS (Levy, 2010). In addition, NBS for hemoglobinopathies and cystic fibrosis can detect healthy carriers who will never develop these diseases.

Multiplex testing methods that have been implemented to detect core NBS conditions can also detect other conditions at no additional cost. These secondary conditions are included on several state NBS panels even though they were not selected as part of the core panel because their natural history, need for treatment, or the efficacy of treatment were not clearly understood ("Newborn screening," 2006). Although these secondary conditions clearly do not meet all of the Wilson and Jungner criteria, their inclusion on NBS panels has helped to identify variability in their natural history and has provided information about treatment that would likely otherwise have remained unknown (Levy, 2010).

With regard to UTS, at least eight of the ten Wilson and Jungner criteria are clearly met. Arguments can be made that insufficient data exist to determine if the following two criteria are met: 1) the test should be acceptable to the population being tested; and 2) the natural history of the condition should be known. With regard to the first unmet criterion, we were

unable to identify any published studies that have reported on the acceptability of UTS among newly diagnosed CRC patients. Nevertheless, a pilot study of CRC patients diagnosed under the age of 50 years found that patients generally felt the advantages of genetic screening/testing outweigh the disadvantages (Landsbergen, Prins, Brunner, & Hoogerbrugge, 2009). With regard to the second unmet criterion, there is some evidence to suggest that the full phenotypic spectrum and natural history of LS is not yet fully understood (Barrow et al., 2008, 2009; Bonadona et al., 2011; Hampel et al., 2005; Stoffel et al., 2009). Tumor screening is therefore expected to identify LS patients who have weak family histories of cancer and do not meet previously established clinical diagnostic criteria (Umar et al., 2004). So, UTS can potentially provide an opportunity to more fully characterize the phenotypic spectrum of LS, just as NBS provided the opportunity to understand the phenotypic spectrum for several genetic conditions (including PKU).

Since the Jungner and Wilson criteria were published, new population screening criteria have emerged that re-frame key issues to reflect changes in medical decision-making (Andermann, 2008; Harris, Sawaya, Moyer, & Calonge, 2011). These newer criteria and their application to NBS and UTS are provided in Table 2. The newer criteria place emphasis on patient autonomy, magnitude of benefits versus harms, equity, and several factors important to successful implementation (i.e., education, program management, quality assurance, and planned evaluation). The following sections discuss many of these issues as they relate to NBS and UTS.

Autonomy and Informed Consent

Nearly all state NBS programs and most UTS programs do not require written informed consent prior to screening, but several provide screening information and an opt-out option (Beamer et al., 2012; Carmichael, 2011; Cohen, 2013). Although informed consent is recommended prior to genetic testing (“Informed Consent,” n.d.), mandatory or opt-out approaches to NBS and UTS have been justified because the risks are low and the potential benefits are high. Additionally, the initial screening tests performed as part of these programs do not typically test DNA for germline mutations; and, in the case of UTS, clinical actions should not generally be taken without further evaluation and diagnostic testing (Carmichael, 2011; Ladabaum et al., 2011; Williams & Williams, 2011). Once a patient is identified with a positive tumor screen, informed consent should be obtained before proceeding with confirmatory germline testing (“Informed Consent,” n.d.)

Although autonomy argues in favor of explicit informed consent prior to screening, it is not the only ethical principle that has been considered in policy making for screening programs. Other important ethical principles include beneficence and nonmaleficence (i.e., provide benefit and avoid harm). Using these principles, mandated NBS has been justified based on substantial benefits that arise from identification and early treatment of conditions (Levy, 2010). However, if conditions do not need emergent diagnosis and treatment, there is less justification for mandatory screening (Ross, 2010). For example, the expansion of NBS to include the identification of secondary conditions (described previously) have opened a debate about the need for parental informed consent (Dhondt, 2010; Kerruish, Webster, &

Dickson, 2008). Although this remains contentious, the need to balance respect for parental autonomy and the promotion of children's health has been recognized (Ross, 2010).

With regard to screening adults for LS or other adult onset genetic conditions, the issue of autonomy is particularly important to consider because the screening population consists of autonomous adults rather than infants. Historically, genetic screening and testing for LS has been performed on adults who actively sought out genetic risk information (Hall, 2010). With UTS programs, particularly those that do not require explicit informed consent, the patient may be confronted with the possibility of a genetic risk factor that he or she is not expecting, did not seek out, and may not even want (Hall, 2010). On the other hand, an opt-out approach may be preferred over explicit informed consent given that the former is expected to: 1) result in more patients undergoing screening; 2) maximize the number of patients identified with LS; 3) ultimately benefit a greater number of individuals; and 4) patient autonomy is honored when they are consented prior to germline genetic testing. Additionally, UTS programs that apply an opt-out approach could potentially result in fewer negative outcomes because the need for explicit consent could create an additional decisional burden for newly diagnosed CRC patients who are already faced with many decisions and challenges (Peres, 2010). The consenting process may also unnecessarily increase anxiety (Peres, 2010). Furthermore, obtaining informed consent is resource intensive and requires knowledgeable individuals to be available to discuss LS with all CRC patients even though most will not have LS (thus taking additional resources that could be used by other important health care programs).

For both NBS and UTS, an opt-out approach may provide a reasonable balance between competing ethical principles. There is evidence of parental support for an opt-out approach with regard to NBS for conditions that do not have available treatments (Rothwell, Anderson, Swoboda, Stark, & Botkin, 2013; Vellinga, Cormican, Hanahoe, Bennett, & Murphy, 2011). Nevertheless, patient acceptability of an opt-out approach or the amount of information desired prior to screening does not appear to have been explored with regard to UTS.

Benefits versus harms

NBS provides clear and substantial benefits to those infants who are identified with disorders for which the treatment is effective when initiated early (Dhont, 2010). For these conditions it is difficult to argue against screening (Dhont, 2010). However, technological advances have led to the inclusion of some conditions for which no clear treatment is established or conditions where many affected individuals remain asymptomatic even without treatment. Screening for these conditions may do more harm in terms of parental anxiety and financial costs associated with follow-up testing and treatments that may not even be beneficial (Dhont, 2010). However, identification of some conditions may still offer benefits to the family (e.g., reproductive decisions, value of knowing what is wrong when symptoms do appear) and benefits to society (e.g., increasing knowledge of rare diseases).

When considering UTS, overall benefits are substantial because family members who are identified with LS through cascade testing have the opportunity to reduce cancer morbidity and mortality through increased cancer surveillance and other risk reduction options (Heikki

J Järvinen et al., 2009; H J Järvinen et al., 2000; Palomaki, McClain, Melillo, Hampel, & Thibodeau, 2009). Although a diagnosis of LS may not alter current cancer treatment for many individuals with CRC, it will influence cancer surveillance recommendations and surgical prevention options to reduce risks for future cancers among CRC survivors. Furthermore, anecdotal reports have indicated that patients are often appreciative of the additional information they obtain from UTS (Peres, 2010).

Despite clear benefits of UTS to both the CRC patients and their family members, it is possible that estimates of benefit in terms of reductions in morbidity and mortality may be overstated. More specifically, if cancer risks in certain families identified through UTS are lower than current estimates and/or if the age of cancer onset is later, a higher cost-benefit ratio may result from applying existing cancer screening protocols for everyone identified through UTS (Bellcross et al., 2011). There is even the potential for harm if individuals with lower cancer risks undergo unnecessary cancer screening and/or preventive procedures that may be of little clinical benefit (Kempers et al., 2011; H. T. Lynch, Lynch, Snyder, & Riegert-Johnson, 2011).

Additional risks of UTS are believed to be minimal (Hampel, 2010). However, prior to UTS implementation, some patients with CRC expressed concern that genetic testing for hereditary CRC may lead to adverse psychological outcomes for themselves or their family members (Kinney et al., 2000; Kinney, DeVellis, Skrzynia, & Millikan, 2001; Lerman, Marshall, Audrain, & Gomez-Caminero, 1996; Ramsey, Wilson, Spencer, Geidzinska, & Newcomb, 2003). Nevertheless, long-term studies have been quite reassuring in terms of psychological outcomes following inherited cancer predisposition testing (Collins et al., 2007; Heshka, Palleschi, Howley, Wilson, & Wells, 2008). Published data on outcomes of clinical UTS programs for CRC patients are limited to a handful of institutions in the United States and patient perceptions were not assessed (Heald et al., 2013; Jin et al., 2013; P. M. Lynch, 2011). During interviews conducted with genetic counselors from 12 centers that have implemented UTS, few negative or unanticipated patient outcomes were identified, including: 1) two patients who were unaware that tumor screening was part of their surgical informed consent; 2) a few patients who were concerned about their inability to pay for genetic counseling and/or germline testing; 3) the need to plan for handling results from prison inmates or deceased patients; 4) rare problems with reimbursement for tumor screening at two institutions; 5) one patient who, despite lack of interest, felt obligated to undergo germline testing (i.e., expressed concern about the lack of perceived autonomy); 6) difficulties among providers in deciding how to follow-up when results are equivocal or atypical; and 7) concerns that physicians were not always disclosing screening results to patients (Cragun et al., 2014). Some of these concerns are similar to those identified in other studies that occurred prior to UTS implementation. For example, patients with CRC in prior studies have expressed concerns about costs associated with genetic testing (Kinney et al., 2001; Ramsey et al., 2003). Confirmatory genetic testing for LS is approximately $1,000 to $4,000 and it is not always covered by insurance (Weitzel, Blazer, MacDonald, Culver, & Offit, 2011). Having a positive screen, but not being able to follow-through with genetic counseling and/or germline testing may invoke anxiety and worry (Heiniger, Butow, Price, & Charles, 2013); therefore, policy efforts are needed to ensure widespread access to appropriate genetic testing services. Furthermore, studies are needed to identify whether

patients perceive any unanticipated harms associated with UTS so that risks can be quantified and minimized.

Equity

Historically, the number and type of conditions screened in NBS programs was highly variable across states before tandem mass spectrometry was widely adopted ("Impact of expanded newborn screening--United States, 2006," 2008; Levy, 2010). Some states were early adopters of MS/MS and screened for >30 conditions, while others screened for only three. However, state screening is now much more uniform ("Impact of expanded newborn screening--United States, 2006," 2008).

Similar to the NBS experience, UTS has not been implemented uniformly; academic institutions have been more likely to have adopted tumor screening (Beamer et al., 2012). In order to be equitable, it will be important for all hospitals and cancer centers to begin screening once the early adopters have shown screening to be feasible, acceptable, and cost-effective in real-world settings. Unless screening becomes wide-spread, health disparities could increase. Unfortunately lack of access to or reimbursement for genetic counseling could limit widespread screening, and continued efforts are needed to address these issues. Furthermore, policy-level efforts are needed to ensure that patients identified with LS have access to cancer surveillance and prevention options that are not always covered by health insurance.

Factors to increase successful implementation and minimize risks

Education, quality assurance, and evaluation efforts are all important for successful implementation of any screening program and can also help to identify and/or minimize risks. Unfortunately, these issues are not always given enough attention before screening is adopted (Dhondt, 2010; Hall, 2010).

The need for education, quality assurance, and evaluation was heightened with the expansion of NBS. Ongoing educational efforts are necessary as illustrated by a U.S. study revealing that the majority of mothers indicate they were not given any information about NBS, were not given enough information, or did not remember whether they were given any information (Hasegawa, Fergus, Ojeda, & Au, 2011).

Quality assurance mechanisms vary across state NBS programs, but a centralized website was created in 2008 for states and countries to input screening data to help refine cut-off values (http://www.clir-r4s.org). Optimal cut-off values are critical to maximize sensitivity (so that cases are less likely to be missed). Cut-off values are also optimized to minimize false positives, which is important given that positive screens can cause substantial parental distress and increase associated screening costs related to follow-up testing (Gurian, Kinnamon, Henry, & Waisbren, 2006; Levy, 2010).

Although it is not clear whether evaluations were planned prior to NBS expansion across the U.S., many states have enacted short-term follow-up programs throughout the years (Feuchtbaum, Dowray, & Lorey, 2010). Furthermore, clinical effectiveness and cost-effectiveness of screening for many conditions have now been established, but evaluation

has been difficult for some of the rarer disorders (Wilcken, 2011). Recently evaluations have begun to assess long-term outcomes of NBS (Berry, Lloyd-Puryear, & Watson, 2010; Feuchtbaum et al., 2010; Singh & Hinman, 2010).

With regard to UTS, cost-effectiveness modeling studies have demonstrated that theoretical costs are comparable to other accepted screening programs (James M Gudgeon et al., 2011; Ladabaum et al., 2011; Mvundura, Grosse, Hampel, & Palomaki, 2010). Nevertheless, UTS may face several challenges to successful widespread implementation, given that institutions are each left to devise their own program and there are few centralized efforts to coordinate implementation on a state-wide level. The Ohio State University's model of state-wide service provision of UTS is promising, but only if resources to sustain it are allocated once their research study is complete ("Statewide Screening Initiative Launched By Ohio State Has Life-Saving Potential," n.d.). Given limited government resources, we expect that screening will continue to spread at the institutional, rather than state, level. Nevertheless, applying state-wide laboratory and follow-up processes similar to those that have been implemented for NBS has been proposed as a potential way to reduce cost and improve standardization, quality of care, and access to genetic counseling by trained health care providers (Bellcross et al., 2011).

The need for health care provider education prior to UTS implementation is illustrated by anecdotal experiences the authors have both witnessed and heard where patients and/or practitioners have misinterpreted a positive screen to mean that the patient has LS before taking a family history or performing additional germline testing necessary to confirm a LS diagnosis. It would also be concerning if practitioners fail to recognize that a negative screen or negative germline test in the context of strong family history does not necessarily rule out LS. This highlights the need for educating stakeholders involved in UTS and for the involvement of professionals with genetics expertise.

Tumor screening results will be positive (demonstrating evidence of MMR deficiency) in approximately 15% of CRC patients who do not have LS (Herman et al., 1998). Fortunately, there are ways to reduce the number of these individuals who will need to follow-through with genetic counseling and germline testing (Jin et al., 2013). Specifically, to minimize potential patient anxiety among those who do not likely have LS, an additional screening test (using *BRAF* or *MLH1* hypermethylation) can be added as an automatic reflex test to rule out LS in a number of patients with MMR deficiency that is not likely the results of a germline mutation (Jin et al., 2013).

Quality assurance of tumor screening is another challenge given that screening is performed in several laboratories. IHC can be difficult and scoring is variable, thus accuracy may be unacceptably low in some settings (Overbeek et al., 2008). Some labs participate in College of American Pathologists (CAP) external proficiency testing. However, participation is not required and IHC testing for MMR gene proteins is not subject to CAP proficiency tests ("Recommendations from the EGAPP Working Group," 2009).

Program evaluation is also essential in order to measure the level of UTS success, minimize risks, and monitor changes in UTS programs. Furthermore, ongoing evaluation can help in

developing evidence regarding best UTS practices and thereby provide guidance to other institutions that may consider UTS adoption. Although many institutions are monitoring their tumor screening programs, survey results indicate that approximately half of institutions that implemented UTS or criterion-based screening lack a tracking system (Cohen, 2013; Beamer, 2012). Comparisons of several programs that are tracking outcomes have been made by the authors and results suggest that substantial variability in patient follow-through with germline testing after a positive screen may be related, at least in part, to differences in procedures that were implemented. However, the validity of institutional comparisons would be improved with a centralized, uniform, tracking system that could help to ensure quality and effectiveness.

Conclusion

To our knowledge this is the first article to detail the extent to which UTS programs designed to identify LS meet criteria for population-based screening programs. Although UTS and expanded NBS programs meet most of the criteria, there are a few criteria that do not appear to be met for all UTS programs or for all conditions included in expanded NBS. By comparing and contrasting NBS with UTS we highlighted the importance of assessing potential benefits and potential harms when new screening programs or new genomic tests are implemented into the U.S. healthcare system. The need to continually evaluate and monitor the implementation of genomic tests is a critical public health need as DNA sequencing enables detection of inherited. predisposition of multiple diseases at progressively lower costs and as the U.S. healthcare system becomes increasingly concerned with cost-effectiveness and quality outcomes.

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Table 1

Application of the Wilson and Jungner Criteria (1968) for Public Health Screening

Criteria	Newborn Screening (NBS)	Universal Tumor Screening (UTS) for Lynch syndrome (LS)
1) The condition should be an important health problem	**Criterion met for most conditions.** Conditions included on NBS panels *have the potential* to lead to serious health problems. However, NBS also detects many patients who would remain asymptomatic even without treatment (Levy, 2010)	**Criterion met.** LS is an important health problem as it confers high risks for a variety of cancers, many of which can be prevented or identified early through increased screening or surgical options (Heikki J Järvinen et al., 2009 ; H J Järvinen et al., 2000).
2) There should be an accepted treatment for patients with recognized disease	**Criterion met for most conditions.** Most of the conditions on NBS panels have an accepted treatment proven to prevent morbidity and/or mortality. However, this is not the case for all conditions (Levy, 2010; Wolff, Nordin, Brun, Berglund, & Kvale, 2011).	**Criterion met for patients who survive initial CRC diagnosis.** Although a diagnosis of LS does not alter current cancer treatment for many individuals with CRC, this may change in the future. Furthermore, it is clear that identifying LS alters cancer surveillance recommendations and surgical prevention options to reduce risks for future cancers.
3) Facilities for diagnosis and treatment should be available	**Criterion met.** State NBS programs generally have designated centers that diagnose and treat conditions identified through NBS. However, access to experienced specialists varies and may require patients to travel if they are in rural areas.	**Criterion met.** Any physician can order tumor screening or germline testing for LS, but they may not always have the knowledge and experience needed to interpret test results in the presence and absence of a family history of cancer, or to provide appropriate counseling and cancer surveillance recommendations. Many hospitals do not have a genetic counselor, but telephone counseling has expanded access to genetic counseling. services.
4) There should be a recognizable latent or early symptomatic stage	**Criterion met in most cases.** In rare cases symptoms can appear before the results of screening and/or diagnostic tests are completed.	**Criterion met.** Although patients with CRC are already symptomatic, there is a latent period for secondary cancers. Additionally, family members may be asymptomatic. Thus, there is a clear opportunity for cancer prevention among both patients and their at-risk relatives.
5) There should be a suitable test or examination	**Criterion met.** NBS tests are generally all highly sensitive if cut-off values are set properly. There are, however, a relatively large number of false positives (Dhondt, 2010; Frazier et al., 2006 ; Gurian et al., 2006). NBS also fails to detect a small number of patients affected with some of the conditions (Frazier et al., 2006).	**Criterion met.** According to EGAPP, the tests are suitable (“Recommendations from the EGAPP Working Group,” 2009). However, reports of the sensitivity and specificity of tumor screening strategies have been somewhat variable, depending on which IHC stains or number of MSI probes are used (Cicek et al., 2011; Loughrey et al., 2007; Shia, 2008 ; Tranø et al., 2010). A small percentage of patients will be missed with IHC or MSI and germline testing fails to identify a mutation in some cases (“Recommendations from the EGAPP Working Group,” 2009).
6) The test should be acceptable to the population	**Criterion met (with some controversy).** Overall support of NBS is high among parents and the general public. However, the issue of whether informed consent should be obtained from parents is controversial, as is the issue of how blood spots can and may be used by the	**Uncertain.** To our knowledge, there are no published studies looking at CRC patients’ perceptions of UTS. However, a pilot study of CRC patients diagnosed under the age of 50 found that the patients felt the “advantages of genetic screening/testing will weigh-

Criteria	Newborn Screening (NBS)	Universal Tumor Screening (UTS) for Lynch syndrome (LS)
	state after screening is complete (Carmichael, 2011 ; Ross, 2010)	up against the disadvantages" (Landsbergen et al., 2009). Patients were apprehensive about having to discuss hereditary cancer with their family (Landsbergen et al., 2009).
7) Adequate knowledge of the natural history of the condition	**Not met for some conditions prior to screening being implemented.** The natural history of a benign variant that increases levels of phenlylalanine was not understood prior to the initiation of NBS for PKU. This resulted in serious harm to infants who had benign hyperphenylalaninemia because they were placed on a diet that was too restrictive (Ross, 2006). Other conditions, such as 3-MCC deficiency, and SCADD were added to NBS before an adequate understanding of the natural history of the conditions existed. However, without including these on NBS, the variability in natural history may not have ever been discovered (Levy, 2010).	**Uncertain.** It is possible that UTS will identify patients from families where the particular gene mutation may be less penetrant (i.e., associated with lower cancer risks than previously identified). If this is the case some patients may receive intensive and invasive cancer surveillance or prophylactic surgery even though their risks for cancer may not be as high as previously estimated. There are already a number of studies suggesting the penetrance of LS mutations is lower than initially reported (Barrow et al., 2008, 2009; Bonadona et al., 2011 ;Hampel et al., 2005; Stoffel et al., 2009). UTS will help to identify patients who would not have been identified based on family history and this, in turn, will help inform the natural history and lifetime cancer risks of Lynch syndrome.
8) An agreed policy on whom to treat as patients	**Criterion met.** NBS was historically set up with the idea that the newborn is the patient, as they stand to benefit the most from NBS. However, identifying a genetic condition in a newborn typically impacts multiple family members who may need subsequent genetic counseling about reproductive risks. Additionally, mothers are occasionally picked up secondary to a positive screen in the newborn.	**Criterion met.** EGAPP acknowledges that UTS will be especially useful for identifying and preventing cancer in at-risk family members who have not yet developed cancer ("Recommendations from the EGAPP Working Group," 2009). Thus, both patients with CRC and their family members will need to be "treated" as "patients."
9) The cost of case-finding should be balanced in relation to possible expenditure on medical care as a whole	**Criterion met for most conditions.** With tandem mass spectrometry, the inclusion of multiple conditions became even more cost effective (Insinga, Laessig, & Hoffman, 2002 ;Thomason et al., 1998). However, costs increase as more conditions are added due to the cost of follow-up for false positives (Levy, 2010).	**Criterion met.** Cost-effectiveness modeling studies have demonstrated that costs are comparable to other accepted screening prevention programs in the U.S. (James M Gudgeon et al., 2011; Ladabaum et al., 2011 ; Mvundura et al., 2010). However, if patient follow-through after a positive screen is low then cost-effectiveness is decreased. Thus, it is critical to track data and identify methods to maximize or improve cost-effectiveness.
10. Case-finding should be a continuing process	**Criterion met.** Given that most screened conditions are autosomal recessive, there is a continuing need to identify affected infants because there is often no prior family history of the condition.	**Criterion met.** This is currently true for UTS. However, as more families with LS are identified, screening may no longer be cost effective.

Table 2

Applying Newer Screening Criteria

Screening criteria (Andermann, 2008)	Newborn Screening (NBS)	Universal Tumor Screening (UTS) for Lynch Syndrome
Screening should respond to a recognized need	**Uncertain.** It has been argued that the wide-scale expansion of NBS occurred in response to technological advances (i.e., tandem mass spectrometry) and/or occurred as a result of pressure from parents and advocacy groups rather than in response to a recognized need by policy makers (Andermann, 2008; Levy, 2010).	**Criterion met.** The need for LS identification is reflected in the Healthy People 2020 provisional objective: "*Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome.*" Reliance on medical and family history information to determine who should be tested for LS misses a substantial proportion of individuals with LS.
Objectives of screening should be defined at the outset	**Criterion met until NBS expansion.** Initially, the objective of NBS was to reduce mental disability through early treatment of PKU. Expanded screening has resulted in the addition of some conditions that have less effective treatments. As a result, the objectives became less clear or other objectives were added (Levy, 2010)	**Criterion met.** EGAPP stated that UTS for LS is primarily intended to reduce cancer risk among relatives of newly diagnosed CRC patients ("Recommendations from the EGAPP Working Group," 2009). However, there are also potential benefits to the patients in terms of preventing additional cancers.
There should be a defined target population	**Criterion met.** All newborns in each state within the U.S.	**Criterion met.** The target for UTS is all newly diagnosed patients with CRC. It is also worth noting that some institutions and individuals have expanded the target population to include screening of all newly diagnosed patients with endometrial cancer (Bellcross et al., 2011).
Program should ensure informed choice, confidentiality, and respect for autonomy	**Not typically.** Due to the legislatively mandated nature of NBS, informed consent has not been a requirement; therefore, this has not been a priority. Although virtually no states require explicit informed consent there is typically an option to "opt out." The majority of mothers in a U.S. study indicated that they were not given any information about NBS, were not given enough information, or did not remember whether they were given any information (Carmichael, 2011 ;Hasegawa et al., 2011).	**Not typically** Survey data suggest that most routine tumor screening programs at institutions do not require informed consent before initial screening, a small percentage provide written information about screening along with other pre- surgical materials, some present a clear option to "opt out" of screening, and very few require written consent (Beamer et al., 2012; Cohen, 2013)
Overall benefits of screening should outweigh the harms	**Criterion met for many conditions screened.** Although NBS is beneficial overall, it now includes some conditions for which no clear treatment is established or conditions where many affected individuals remain asymptomatic even without treatment (Levy, 2010; Ross, 2006). Screening for these conditions could, in some cases, do harm in terms of parental anxiety and wasted resources.	**Criterion met.** UTS clearly has potential benefits with few anticipated harms. However, to our knowledge, there has been no large scale attempt to identify unanticipated or harmful outcomes. There have been anecdotal reports of substantial psychological distress following a positive screen. This, again, highlights the need for education and training of professionals involved in UTS.
Program should promote equity and access to screening	**Criterion met, but historical inequities have existed.** Historically, the number and type of conditions screened was highly variable across	**Not met.** Inequities currently exist across the U.S. because only certain institutions have chosen to enact UTS. It will be important to get all hospitals

Screening criteria (Andermann, 2008)	Newborn Screening (NBS)	Universal Tumor Screening (UTS) for Lynch Syndrome
for the entire target population	states before tandem mass spectrometry was widely introduced (“Impact of expanded newborn screening--United States, 2006,” 2008 ; Levy, 2010). Some states were early adopters and screened for over 30 conditions, while others screened for only three. However, this has changed and state screening is now much more uniform (“Impact of expanded newborn screenine--United States, 2006,” 2008).	and cancer centers on board once the early adopters have shown screening to be feasible, acceptable, and cost-effective in real-world settings. Unless screening is wide-spread, health disparities could increase.
Screening program should integrate education, testing, clinical services and program management	**Criterion met.** Education, testing, clinical services, and program management have been integrated into state NBS programs. However, processes vary significantly by state; the expansion of NBS has necessitated ongoing educational efforts.	**Criterion met at some, but not all institutions.** Each institution is devising their own tumor screening program given the lack of centralized or state-wide programs.
There should be quality assurance and mechanisms to minimize potential risks of screening	**Criterion met.** Many of the quality assurance mechanisms that helped to determine best practices (i.e., the best cut-off values to maximize sensitivity and minimize false positives) occurred after NBS programs were established. Minimizing false positives is critical due to the parental distress that positive screens cause (Gurian et al., 2006). A website was created in 2008 where states and countries can input their screening data, which is then used to help refine cut-off values (www.region4genetics.org). Data entry is voluntary and without compensation, but there are a many participating groups who feel the effort is worthwhile due to the potential to improve patient outcomes.	**Uncertain.** Some labs participate in CAP external proficiency testing. However, participation is not required and IHC testing for MMR gene proteins is not subject to CAP proficiency tests (Overbeek et al., 2008 ; “Recommendations from the EGAPP Working Group,” 2009). Patients and/or practitioners may misinterpret a positive screen to mean that the patient has LS before taking a family history and performing additional testing to confirm a diagnosis. It would also be concerning if practitioners fail to recognize that a negative screen or negative germline test in the context of strong family history does not necessarily rule out LS. Thus, education will be an important key to minimize potential risks.
Program evaluation should be planned from the outset	**Uncertain.** Although it is not clear if evaluations were planned prior to implementation, many states have enacted short-term follow-up programs throughout the years (Feuchtbaum et al., 2010). Furthermore, clinical effectiveness and cost-effectiveness of screening for many conditions has been established, but evaluation has been difficult for the rarer disorders (Wilcken, 2011). Recently evaluations have begun to assess long-term outcomes of NBS (Berry et al., 2010 ; Feuchtbaum et al., 2010; Singh & Hinman, 2010)	**Criterion met for some but not all programs.** Although some programs are evaluating their tumor screening programs, many report lacking a tumor screening tracking system. A tracking system is clearly needed to ensure that screening is effective.