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Review Article

Lynch Syndrome Genetic Testing as an Exemplar of Translational Research as a Whole

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Abstract

The majority of studies involving translational research focus on the assessment of useful molecular mechanisms leading to basic scientific discoveries capable of being translated into diagnostic and therapeutic interventions. Often the full scope of translational research – from bench-side discovery to clinical and community application and assessment of cost-effectiveness – gets lost in this initial focus. In this review we consider the development of genetic testing for Lynch syndrome, the most prevalent hereditary form of colorectal cancer, as an exemplar representing all the key phases of translational research. The details of each research stage and respective creative developments are examined, leading up to recent work at the T4 outcomes research stage. The review concludes with questions of implementation in the current healthcare environment.

Keywords: Lynch syndrome; Hereditary nonpolyposis colorectal cancer; Genetic testing; Genetic screening; MSI testing; IHC testing; Mismatch repair gene; Translational research; Public health; Clinical validity; Clinical utility; Clinical guidelines; Cost-effectiveness

Introduction: The Levels of Translational Research

The last decade has witnessed tremendous growth in translational research, with the U.S. National Institutes of Health currently awarding Clinical and Translational Science awards to more than 50 research institutions in 31 states [1]. At the same time, studies of the "natural history" of promising therapeutic or preventive interventions have shown that only ~5% of "highly promising" basic science findings become licensed for clinical use, and only 1% are used for the licensed indication [2,3]. The Annals has published exciting articles demonstrating the basic science behind molecular developments pointing the way to therapeutic and diagnostic techniques. It is vital to hold in mind that basic science discoveries will eventually move through what Khoury et al. of the U.S. Centers for Disease Control and Prevention (CDC) label a "continuum" of translational research on the way to promising application [2]. T1 translation research aims to move a basic biomedical discovery into a candidate health application (clinical or genetic test/therapeutic intervention). T2 translation research evaluates the value of a given application for health practice, leading to the development of evidence-based guidelines (clinical or population level). T3 translation research seeks to move evidence-based guidelines into health practice through research into dissemination, implementation, and widespread diffusion of the technology. T4 translation research is geared towards the evaluation of "real world" outcomes, which includes assessment of morbidity and mortality, quality-of-life indicators, and cost-effectiveness.

Phases 1 and 2 of Lynch syndrome translational research

The attention devoted to the mechanisms and management of hereditary nonpolyposis colorectal cancer or Lynch syndrome (LS) by the basic science, medical and public health communities serves as an exemplar of progress through the various stages of translational research. LS is the most common heritable cause of colorectal and endometrial cancer (1/35 CRC and 1/40 EC cases, respectively) [4]. LS genetic mutations carry a 40-80% lifetime risk of developing colorectal cancer (CRC), and are associated with at least seven other cancer types (e.g., endometrial, intestinal, ovarian, stomach) [5].

While the initial observations of the syndrome and its family clustering first took place at the University of Michigan as early as 1895 and under Henry T. Lynch in 1971, the era of basic genetic discovery spanned 1993 through 2004, the year in which a comprehensive mutational database was established [6]. Major scientific milestones included linkage analysis of the first genetic locus for LS and the discovery of microsatellite instability in human tumors in 1993, positional cloning of responsible genes (*MSH2, MLH1, PMS2, MSH6* and others) from 1994 onwards, and the discovery of *MLH1* epigenetic defects in 2002. The discovery process showed various transitions between basic laboratory (yeast and bacteria) models and humans, rapid adoption of genetic technology (gene mapping, positional cloning, gene sequencing), and high levels of collaboration. Genetic epidemiology was needed to characterize the phenotypic heterogeneity of the germline mismatch repair (MMR) gene defects, and to correlate pathogenicity with mutations in affected families.

The discovery of the responsible genetic defects and their presentation led to the development of means of assessment. The CDC-supported Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group performed a systematic review in 2009 of the analytical and clinical validity, and clinical utility of three forms of preliminary tumor testing (microsatellite instability (MSI) testing, immunohistochemistry (IHC) testing, and *BRAF* mutation testing) that determine suitability for conclusive MMR gene mutation testing in a given case [7]. EGAPP found adequate evidence to extrapolate the clinical sensitivity and specificity of

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these preliminary screens and compare four select combined testing strategies, though the Working Group noted further early-stage population research comparing MMR testing and preliminary screening results would have strengthened the findings even further.

The development and promulgation of clinical guidelines is an important process for the adoption of a biomedical technology once it has passed muster. The clinical guidelines for Lynch syndrome have come in three waves, each further articulating and refining the use of genetic testing. Most of the clinical guidelines for Lynch syndrome are based on the Amsterdam Criteria and Bethesda Guidelines, which were developed and disseminated in the early 1990s [5,6]. The Revised Bethesda Guidelines, which specify the circumstances under which a person should undergo MSI testing for a CRC, came out in 2004, and other CRC risk assessment tools able to identify cases with likelihood of an hereditary component also emerged around that time [8,9]. Currently the Amsterdam II/Revised Bethesda Guidelines are used to select patients with CRC for IHC analysis and/or MMR genetic testing. Part of the success of the guidelines may be attributed to the involvement of expert groups such as the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the American Gastroenterology Association (AGA) in their development and dissemination [5]. Calls for "universal screening" of CRC patients to detect LS started in 2008, with major consensus-building efforts to yield recommendations for universal screening, which could also lead to screening of high-risk relatives, beginning in 2010 [10-12].

Phases 3 and 4 of Lynch syndrome translational research

At the T3 translation research level, studies in the U.S and abroad have demonstrated uptake by family members of genetic testing for LS and of procedures for universal testing of CRC cases. Palomaki et al. describe a study in Finland looking at LS testing in 252 family members and 22 index cases selected initially by family history [13]. One hundred thirty-three family members chose colonic examination; 78 chose to forgo clinical screening, and all subsequent cases of CRC underwent genetic testing. In seven studies looking at provision of genetic counseling and testing to LS families, about half of relatives received counseling, and 95% of these individuals chose to have MMR genetic testing [7]. In 2011 leading cancer institutions and public health agencies in the U.S formed the Lynch Syndrome Screening Network (now containing 85 member organizations), which in turn formed an LSSN database to allow exploration of key gaps in universal screening implementation [14]. This network and individual institutions are in the process of developing protocols and descriptive data on the implementation of universal LS screening procedures among CRC cases [14,15].

T4 translational research examining "real world" outcomes is quite vigorous at this point. Psychosocial research looking at the impact of LS genetic testing on probands and their families is beginning to catch up to the earlier literature covering the consequences of a positive *BRCA1/2* diagnosis in families with a history of hereditary breast and ovarian cancer. A 2015 University of Toronto study found that most individuals undergoing LS genetic testing were able to adapt to their genetic testing results over time, and continue to successfully engage in long-term monitoring [16]. Surprisingly, 25% of those testing negative showed moderate depressive symptoms on the Center for Epidemiologic Studies for Depression Scale, and were felt by the authors to require added psychosocial support. The research demonstrates the importance of attention to clinical subsets. The consensus conferences to date, both in the U.S and Europe, have pooled together and published in summary form study findings on surveillance and surgical outcomes of multiple organ systems, including the results of prophylactic hysterectomy and bilateral salpingo-oophorectomy, and colectomy, and resultant morbidity [10,11]. Recommendations have tended on the conservative side. Most importantly, comprehensive cost-effectiveness analyses are emerging. In 2015 Scott Grosse of the CDC examined seven LS studies from the U.S and Europe looking at medical/surgical follow-up and universal or "near universal" testing of LS relatives with CRC, and found that all but one displayed incremental cost-effectiveness ratios less than $100,000 per life-year or quality-adjusted life-year gained [17]. In 2016 Chen et al. closed the geographic gap by calculating incremental cost-effectiveness ratios for four LS testing strategies with data from Taiwan – results were cost-effective for the three strategies combining MMR gene sequencing with preliminary tumor testing [18].

Conclusion: The Circle and Trajectory of Translational Research

Lynch syndrome genetic testing represents translational research come full circle – from bench science to population intervention. One could not expect this level of development for the wider range of disease categories today for which genetic tests are being developed, but LS does serve as an exemplar to be followed. Epidemiologic research enters at each stage, from examination of genetic variation and evaluation of test validity and utility, to assessment of population morbidity (and mortality in surgical instances and for final disease outcomes). Having considered the breadth of translational research in this area, one is left to ponder how far healthcare reform can move the actual employment of LS testing to prevent CRC into clinical and community reality, and the role of stakeholders in promoting the needed implementation. Conversely, one might ask, "How can the example of LS translational research help inform the current healthcare environment?".

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