ARCHIMEDES
Quantifying Healthcare

Case Study

Disease Modeling

Client Objective

To test the hypothesis that targeted genetic screening for Lynch syndrome (a genetically heritable cancer syndrome) would be cost-effective and would lead to improved health outcomes when applied to the broad population. If so, the objective was to publish the results, disseminate the findings, and influence opinion leaders and policy makers regarding a new screening strategy for this condition.

Introduction

Lynch syndrome (LS) is a genetically inherited predisposition to multiple types of cancer including colorectal, endometrial, liver, urinary tract, and others. About 2-4% of all diagnosed colorectal cancers and 2-5% of all diagnosed endometrial cancers are due to LS. Despite mutation carrier prevalence in the general U.S. population estimated to be in excess of 1 in 440,[1] the condition remains clinically under-recognized. Current guidelines recommend that a diagnostic workup for LS begin at the time that an individual presents with malignancies that are clinically suspicious for LS, rather than prior to the development of cancer.[2] If individuals with high pre-test probabilities can be detected and genetically screened before the development of malignancies, such early detection followed by frequent cancer surveillance and early intervention may prove to be beneficial in terms of health outcomes and cost effectiveness. A real clinical trial to determine the health outcomes and cost effectiveness of such a screening strategy, however, would require an enormous number of enrollees, and take decades to run. Therefore, Archimedes developed a mathematical model of LS and a five-generation family pedigree model representative of LS in the U.S. population to determine (i) whether primary genetic screening for LS leads to improved health outcomes, (ii) whether such a strategy is cost effective, (iii) an appropriate age to initiate screening by risk assessment, and (iv) an optimal pre-test probability threshold at which to offer genetic testing.

Methods

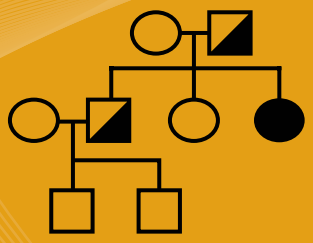
Archimedes recruited a steering committee of five world-renowned LS experts from academia to support the development of the LS model. The model captured the natural history of colorectal cancer and endometrial cancer in carriers of LS mutations and the effects of prevention/surveillance activities (e.g. colonoscopy) and treatments (e.g. surgery, chemotherapy, radiation therapy) on patient outcomes. It also accounted for a five-generation family history of all LS-related cancers to allow the accurate representation of the risk of carrying an LS mutation based on family history. Archimedes used the model to conduct a virtual clinical trial consisting of 100,000 individuals in each of 20 intervention arms compared to current practice. These arms were characterized by (i) different screening ages for starting risk assessment and (ii) different pre-test probability thresholds above which to implement genetic testing. Outcome measures included reduction in colorectal and endometrial cancer incidence, number of tests needed to identify one additional mutation carrier, quality-adjusted life years (QALYs) gained, absolute life years gained, and cost effectiveness.

Results

Pre-test risk assessment starting at ages 25, 30, or 35, followed by genetic testing of those with mutation risks exceeding 5%, was predicted to reduce colorectal and endometrial cancer incidence in mutation carriers by approximately 12.4% and 8.8% respectively. For a population of 100,000 individuals containing 392 mutation carriers, this strategy increased QALYs by approximately 135 with a favorable average cost-effectiveness ratio of $26,000/QALY (Figure). These results suggest that primary screening of individuals for gene mutations, starting with

"The return on our investment for the work done by Archimedes was exceptional. Their expertise, spanning a range from the finest of scientific details all the way up to generating influential results and a national spotlight will continue to benefit Myriad and the patients we serve for some time to come."

Richard Wenstrup, MD
Chief Medical Officer
Myriad Genetic Laboratories



Archimedes, Inc.
123 Mission, 11th Floor
San Francisco, CA 94105
415.490.0400
415.490.0399 (fax)

info@archimedesmodel.com
www.archimedesmodel.com

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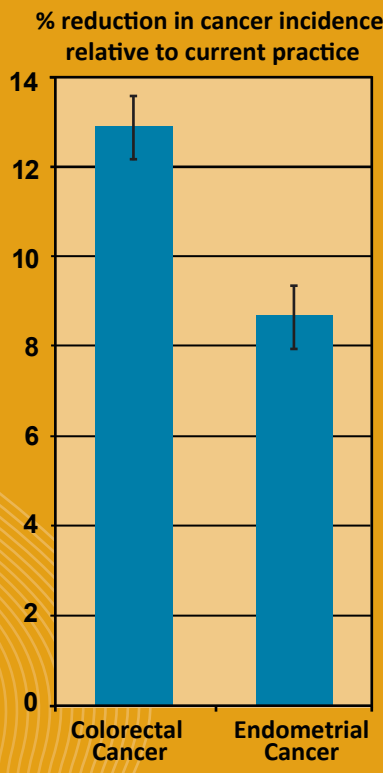

risk assessment between the ages of 25 and 35, followed by genetic testing of those whose risk exceeds 5%, is a strategy that could improve health outcomes in a cost-effective manner relative to current practice.

Implications for public health

The study indicated that the cost effectiveness of primary genetic screening for LS is on par with other cancer-prevention strategies in widespread use by clinicians for the general population, such as colorectal cancer screening, cervical cancer screening, and breast cancer screening. This finding supports the concept that genetic screening of unaffected at-risk individuals, when conducted in association with appropriate risk assessment and followed by surveillance for colorectal and endometrial cancer, would cost effectively improve health outcomes. Furthermore, it offers an evidence-based justification for a shift in the clinical approach to LS from one that is reactive to proactive. By providing clinicians with a simple and easily employed means of determining an individual's future risk of developing LS, the primary care practitioner may now participate with oncology and surgical specialists in the fundamental roles of prevention, surveillance, and management of patients with LS mutations.

Benefits to the client

The results of the study were published in the January 2011 issue of the American Association of Cancer Research (AACR) journal, Cancer Prevention Research[3], and were presented in a nationally broadcast press conference hosted on November 18, 2010, by AACR's president, Dr. Judy Garber, with the participation of Dr. Henry Lynch and several other key opinion leaders. This study is currently influencing practice guidelines regarding screening for heritable colorectal and endometrial cancers.

References

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[2] Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med. Jan 2009;11(1):42-65.

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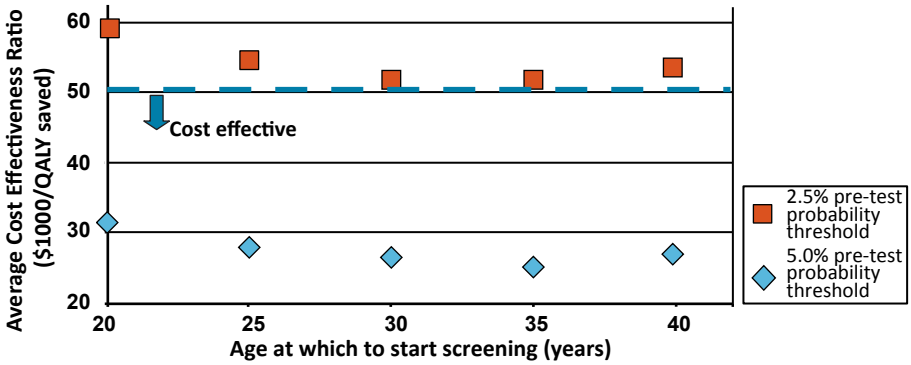

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