Randomized Controlled Trials in Hereditary Cancer Syndromes

Chethan Ramamurthy, MD[a], Yana Chertock, MA[b], Michael J. Hall, MD, MS[b,*]

KEYWORDS

• Hereditary cancer syndromes • Clinical trials • HBOC • FAP • Lynch • HNPCC • Germline mutations

KEY POINTS

- The increase in the recognition of the genetic risk of cancer makes clinical trials in hereditary cancer syndromes important.
- It is challenging to conduct clinical trials in hereditary cancer syndromes because of genetic heterogeneity, established patterns of care, and patient-related factors.
- In hereditary breast and ovarian cancer, randomized controlled trials are few, with most guideline recommendations based on, at best, prospective cohort studies.
- In familial adenomatous polyposis, most randomized controlled trials have focused on chemoprevention, using nonsteroidal antiinflammatory drugs, aspirin, and other agents.
- In Lynch syndrome, there are few randomized controlled trials, with some data on endoscopic surveillance techniques and aspirin for chemoprevention.

INTRODUCTION

Individuals found to have germline mutations in genes that increase the risk of adult-onset cancer constitute a rare but growing population of patients with cancer and at-risk unaffected (ie, no history of cancer) persons. Studies examining germline mutations detected from tumor genomic profiles using next-generation sequencing (NGS) technologies suggest that anywhere from 3% to 15% of patients with cancer may harbor a germline mutation in a hereditary cancer risk gene.[1–4] Although few studies have evaluated this question on a large scale in the average-risk population, these studies paired with mutation prevalence estimates suggest that perhaps 3%

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[a] Department of Medical Oncology, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111-9972, USA; [b] Department of Clinical Genetics, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111-9972, USA
* Corresponding author.
E-mail address: Michael.Hall@fccc.edu

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to 5% of the population carries a germline mutation in a moderate or high penetrance hereditary risk gene that increases cancer risk and affects cancer screening frequency based on current guidelines.[5–7] In the age of increasingly broad (ie, NGS-based multigene panel testing and whole-exome/genome sequencing) and inexpensive genetic testing in tumors and in the germline, the relevance of randomized trials that evaluate the efficacy of various medical treatments in individuals with germline mutations in hereditary cancer risk genes must be appreciated.

Individuals with germline mutations in hereditary cancer risk genes are a heterogeneous population that includes patients with active cancer, survivors, and unaffected patients at risk of cancer. With changing approaches to genetic testing and in particular the growing use of multigene hereditary panels, mutation carriers can have a variable degree of family history that accompanies their genetic risk, from highly penetrant families with many cancers to patients who have little to no cancer in their families. Such population heterogeneity can make design and recruitment to randomized controlled trials (RCTs) challenging, because these studies are often focused on disease prevention and screening-related end points, including detection and prevention of new cancers, and prevention of precancerous neoplasia (eg, adenomas in colorectal cancer [CRC]). The outcomes of these trials are often evaluated many years in the future, and thus study retention is difficult. At-risk individuals are often less aware of trials than patients with cancer, whereas oncologists generally have less interaction with at-risk individuals than with patients with cancer.[8] In addition, healthy individuals, even those at high risk, may be less motivated to participate in a study in which frequent follow-up, surveys, and other time burdens are required. However, those more willing to participate may have high perceived risk of cancer coupled with anxiety and cancer worry, and these traits may diminish their willingness to participate in a randomized study, especially if a placebo arm is involved.

Another challenge in hereditary cancer risk assessment is the growing number of genes of moderate to low-moderate penetrance that are now included on commercially available gene panel tests.[9,10] Although the years of 1995 to 2013 provided a fairly stable time of single-gene and oligogene testing in which RCTs could be more easily accrued and conducted in *BRCA1/2*, adenomatous polyposis coli gene (*APC*), Lynch mutation carriers, the past 3 years have seen a proliferation of new genes, many conferring only moderate risks of cancer in carriers. Making matters more complicated, many of these new genes lack randomized data to support effective clinical management for mutation carriers. In this setting, clinical care is often guided by risk magnitude alone, and management of organ-specific risk is based either on expert recommendations or extrapolated clinical trial data from other genes. For example, providers may question the benefit of prophylactic bilateral oophorectomy in a 40-year-old woman found to carry a mutation in a gene called *BRIP1*, which confers a lifetime risk of ovarian cancer 3 to 4 times that of average-risk women (~4–5%), or the rationale for early and/or increased colonoscopy screening in monoallelic *MUTYH* carriers who harbor ~2-fold increased risk of CRC.[11–14] It seems unlikely that RCTs will be able to keep pace to evaluate screening, prophylaxis, and prevention end points in every new gene discovered and incorporated in a modern gene panel. In the era of inexpensive and power genomic tests, clinicians will increasingly face decisions absent of immediate RCT data specific to the gene mutations found in individual patients, and will rely more heavily on guidelines and recommendations from expert groups and societies.

This article reviews and highlights notable RCTs from the 3 areas of hereditary cancer risk in which most RCTs have been conducted: familial adenomatous polyposis (FAP) and *APC* mutation carriers, hereditary breast ovarian cancer and *BRCA1/2*