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# Cost Analyses of Genomic Sequencing: Lessons Learned from the MedSeq Project

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ABSTRACT

**Objective:** To summarize lessons learned while analyzing the costs of integrating whole genome sequencing into the care of cardiology and primary care patients in the MedSeq Project by conducting the first randomized controlled trial of whole genome sequencing in general and specialty medicine. **Methods:** Case study that describes key methodological and data challenges that were encountered or are likely to emerge in future work, describes the pros and cons of approaches considered by the study team, and summarizes the solutions that were implemented. **Results:** Major methodological challenges included defining whole genome sequencing, structuring an appropriate comparator, measuring downstream costs, and examining clinical outcomes. Discussions about solutions addressed conceptual and practical issues that arose because of definitions and analyses around the cost of genomic sequencing in trial-based studies. **Conclusions:** The MedSeq Project provides an instructive example of how to conduct a cost analysis of whole genome sequencing that feasibly incorporates best practices while being sensitive to the varied applications and diversity of results it may produce. Findings provide guidance for researchers to consider when conducting or analyzing economic analyses of whole genome sequencing and other next-generation sequencing tests, particularly regarding costs.

*Keywords:* cardiomyopathy, costs, humans, hypertrophic, pilot study, primary health care, random allocation, whole genome sequencing.



## Introduction

Advancements in next-generation sequencing (NGS) have made it feasible to integrate whole genome sequencing (WGS) into patient care at a population level, and may streamline the practice of medicine [1]. Currently, genomic testing begins by testing symptomatic patients with panels of genes in which mutations are most likely to explain the disorder. If no causal variants are identified, physicians may order additional tests to examine other candidate genes, a process that can continue until options are exhausted. WGS allows all candidate genes to be examined at once, including regulatory domains and genes that are not typically tested. In addition, WGS information can influence medication choices, inform reproductive decisions, facilitate targeted prevention, and more [2,3]. Moreover, it can be re-queried for diagnostic and treatment purposes as new needs arise. The ability of WGS to provide information with lifelong utility provides a compelling rationale for its use at a population level.

Nevertheless, many commentators also fear the cost and budgetary implications of integrating WGS into regular medical practice [4–7]. It can be many times more expensive than targeted tests and typically has lower sensitivity for identifying certain types of variants than other types of genomic tests [8]. WGS also tends to identify more variants of uncertain significance that can require additional clinical workup, and WGS can provide secondary findings that are unrelated to the test indications but may motivate follow-up testing and long-term screening.

To understand the impact of integrating WGS into the everyday care of sick and healthy populations, we conducted the MedSeq Project, the first randomized controlled trial of WGS in cardiology and primary care settings [9]. In addition to describing the molecular yield and clinical impact of disclosure [10,11], we used microcosting and gross costing methods to report the

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short-term costs of integrating WGS into clinical practice, including its impact on short-term health care utilization and other health sector costs [12]. Findings showed an incremental cost of approximately $5000 to integrate WGS into patient care in 2015, no noticeable impact on downstream health care utilization for a 6-month time horizon, and less than $200 per patient to disclose secondary findings.

The purpose of this article is to discuss key methodological challenges that arose in that cost analysis because of the unique characteristics of WGS. The lessons we summarize and the solutions we adopted provide practical guidance and points to consider as researchers and policymakers develop and interpret cost analyses of WGS and NGS tests more broadly.

## Methods

The methods of the MedSeq Project have been described in detail previously, including the rationale and design of the study [9], the approach to WGS, variant analysis and reporting [13,14], and the rationale and design of the cost analyses [15]. Key terms that are used in this case report are summarized in Table 1. Briefly, the MedSeq Project was a set of parallel randomized pilot trials to examine two archetypal scenarios for integrating WGS into clinical care. The first, *disease-specific genomic medicine*, used WGS to identify molecular causes for disease in patients with family histories or symptoms suggestive of a genetic disorder. To examine this scenario, we enrolled cardiologists and patients with diagnoses of hypertrophic or dilated cardiomyopathy. The second scenario, *general genomic medicine*, used WGS to screen for genetic disorders to enhance disease prevention and to improve medical and personal decision making. To examine this scenario, we enrolled primary care physicians and ostensibly healthy patients.

After consenting to the study and completing a baseline survey, patient participants were randomized to meet with their providers and review health information that included or omitted WGS. Participants were then followed for 6 months. Data relevant to the cost analyses were collected from surveys of providers and patients, medical records and administrative data.

Key challenges that are summarized here were identified by consensus of the investigators who led the cost analyses. We focused on decisions that had a large impact on our analyses and would be applicable to future cost analyses of WGS and other NGS tests. We also highlight issues for which recent developments may change future analyses.

## Results

We identified three key challenges in conducting cost analyses of WGS: defining the test, developing appropriate comparators, and assessing downstream costs. We additionally describe challenges to collecting data about clinical outcomes.

### *Challenge 1: Defining Whole Genome Sequencing*

The first challenge we addressed was to define how we would implement WGS. Decisions about whether to conduct singleton testing or test multiple family members, what sequencing system ("platform") to use, and the minimum coverage that WGS should achieve can have a large impact on costs and molecular yields [2,8]. Professional groups such as the American College of Medical Genetics and Genomics (ACMG), the Association for Molecular Pathology, and the College of Medical Pathologists have been developing standards for WGS [16–18], and the optimal approach depends on the purpose of testing, time frame for results, patient characteristics, and more. Even when a consensus approach exists, many aspects of WGS still vary from setting to setting. Here, we focus on decisions about conducting WGS that had a significant impact on costs and molecular yields in the MedSeq Project but might be made differently in future work. These decisions are summarized in Table 2.

**Table 1 – Key terms used in this case report.**

| | |
|---|---|
| Whole genome sequencing (WGS) | A laboratory process that is used to determine nearly all of the approximately 3 billion nucleotides of an individual's complete DNA sequence, including noncoding sequence. Here, we include bioinformatics analyses to identify health-relevant information, and reporting of these findings to health care providers and their patients. |
| Variant | An alteration in the most common DNA nucleotide sequence. The term *variant* can be used to describe an alteration that may be benign, pathogenic, or of unknown significance. |
| Coverage | The number of times a nucleotide is read during sequencing. |
| Singleton testing | A genetic testing strategy that examines the DNA of a patient alone. |
| Trio testing | A genetic testing strategy that examines the DNA a patient along with the DNA of parent, usually to identify variants that are present in a sick patient that are absent in healthy parents. |
| Deletion | A type of genetic change that involves the absence of a segment of DNA. It may be as small as a single base but can vary significantly in size. |
| Insertion | A type of genetic change that involves the addition of a segment of DNA that can be as small as a single base. |
| Translocation | A type of chromosomal abnormality in which a chromosome breaks and a portion of it reattaches to a different chromosomal location. |
| Sanger sequencing | A low-throughput method used to determine a portion of a patient's nucleotide sequence. This method is well-validated, and has high sensitivity and specificity for identifying variants. |
| Structural variant | A type of large genetic change (i.e., approximately 1000 base pairs or larger in size). This change can include an inversion (a segment of a chromosome that breaks off and reattaches in the reverse direction), a translocation, an insertion, or a deletion. |
| Single-nucleotide polymorphism | A type of variant present in at least 1% of the population where a single nucleotide in the genome sequence is altered. |

Definitions were adapted from the NCI Dictionary of Genetics Terms [66] and from published literature [67]. Terms are presented in the order which they appear in the case report.