Challenges, Ethics, and Cost-Effectiveness of Using Whole Exome Sequencing for Chemoprevention Assessment

Ashwini Badhe

Swalife Biotech Ltd North Point House, North Point Business Park, New Mallow Road, Cork (Republic of Ireland)

Corresponding author Email: info@swalifebiotech.com

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Abstract

Whole-exome sequencing (WES) has emerged as a powerful tool for enhancing cancer chemoprevention by enabling genomic risk stratification, pharmacogenomic tailoring, and mechanistic insight beyond traditional clinical risk models. This comprehensive review evaluates the feasibility, ethical considerations, regulatory landscape, and cost-effectiveness of implementing WES in cancer prevention settings. We synthesize evidence demonstrating that WES can identify high- and moderate-penetrance germline variants, inform polygenic risk assessment, and guide personalized chemoprevention and surveillance strategies, particularly in enriched high-risk populations. However, widespread adoption is constrained by substantial infrastructure requirements, challenges in defining evidence-based surveillance intervals, and unresolved ethical issues surrounding incidental findings, informed consent, genetic discrimination, and equity across diverse ancestries. Regulatory frameworks for WES-guided prevention remain heterogeneous and continue to evolve, while economic evaluations suggest context-dependent cost-effectiveness influenced by population risk, healthcare system structure, and downstream intervention costs. We propose an integrated, equity-centered implementation framework emphasizing standardized risk protocols, genetic counseling integration, transparent consent processes, and prospective evidence generation to responsibly advance WES-guided precision chemoprevention.

Keywords: Whole exome sequencing, chemoprevention, cancer risk assessment, cost-effectiveness, ethical issues, feasibility, sampling intervals, regulatory guidance, precision medicine

1. Introduction

1.1 Background and Clinical Context

Cancer remains a leading cause of morbidity and mortality globally, with approximately 19.3 million new cancer cases and 10 million cancer deaths estimated in 2025[1]. While treatment advances have improved survival for many cancer types, primary prevention through chemoprevention the use of pharmacological or dietary agents to reduce cancer incidence in individuals at elevated risk offers a complementary approach with potential population-level impact[2]. Chemoprevention has demonstrated efficacy in multiple settings: tamoxifen and aromatase inhibitors reduce breast cancer risk in high-risk women[3]; aspirin reduces colorectal cancer incidence[4]; and finasteride reduces prostate cancer risk, particularly high-grade disease[5].

Traditional risk stratification for chemoprevention eligibility has relied on clinical and demographic factors (age, family history, prior benign breast disease, etc.) combined with clinical risk assessment models (e.g., Gail Model for breast cancer, Claus Model for hereditary ovarian cancer)[6]. However, this paradigm has significant limitations: risk models often exhibit moderate predictive accuracy (area under the curve 0.55–0.70 in many contexts); they fail to capture the complexity of genetic predisposition distributed across multiple common and rare variants; and they do not inform drug selection based on pharmacogenomic principles or personalized mechanistic understanding of an individual's cancer biology[6].

Whole exome sequencing (WES) the targeted sequencing of the protein-coding portion of the human genome, encompassing approximately 1.5% of total genomic DNA but containing ~85% of disease-associated variants offers a fundamentally different approach[7]. By comprehensively analyzing variants across thousands of cancer-related genes simultaneously, WES can identify: (1) pathogenic variants in high-penetrance predisposition genes (BRCA1/BRCA2, MLH1, MSH2, etc.); (2) combinations of common variants (polygenic risk scores) associated with modest but meaningful elevation in cancer susceptibility; (3) pharmacogenomic variants that predict chemoprevention efficacy and tolerability; and (4) somatic mutations in accessible tissues (when applied to blood-derived DNA) that may have preventive implications[7].

1.2 Potential Benefits and Promises of WES in Chemoprevention

The theoretical advantages of WES-guided chemoprevention assessment are compelling[8]:

Enhanced Risk Prediction: WES enables construction of comprehensive genomic risk profiles incorporating pathogenic germline variants, polygenic risk scores, and pharmacogenomic information. Studies demonstrate that WES-derived risk scores predict cancer incidence more accurately than traditional clinical models in enriched populations[8].

Precision Chemoprevention: Pharmacogenomic data from WES can guide selection of chemoprevention agents most likely to be effective and well-tolerated for individual patients. For example, CYP2D6 metabolizer status predicts tamoxifen efficacy in breast cancer prevention[9].

Cascade Testing Opportunities: Identifying pathogenic variants in probands enables testing of first-degree relatives, expanding cancer prevention opportunities across families[10].

Mechanistic Understanding: WES results provide insights into individual molecular cancer mechanisms, potentially informing development of targeted prevention strategies[11].

1.3 Challenges and the Impetus for Comprehensive Review

Despite these theoretical benefits, several factors have limited WES adoption in cancer prevention[12]:

Technical and Feasibility Issues: Implementation of WES in clinical prevention settings requires infrastructure for sample processing, bioinformatic analysis, variant interpretation, and clinical reporting. Sampling intervals for surveillance of high-risk individuals remain poorly defined. Integration of WES results with clinical workflows remains challenging[12].

Ethical Complexities: WES analysis generates numerous incidental findings variants in disease-associated genes unrelated to the indication for testing creating ethical dilemmas regarding disclosure obligations, patient autonomy, and psychological burden[13]. Genetic discrimination concerns persist despite regulatory protections like the Genetic Information Nondiscrimination Act (GINA)[13].

Economic Uncertainty: Cost-effectiveness evidence for WES in cancer prevention remains limited. While WES costs have declined dramatically (from ~$1,000–2,000 per sample in 2013 to ~$300–500 in 2025), total program costs must account for interpretation, counseling, surveillance, and chemoprevention interventions, creating uncertainty about cost-effectiveness in different healthcare contexts[14].

Regulatory Ambiguity: FDA regulation of WES-based clinical testing has evolved substantially, with recent emphasis on laboratory-developed tests (LDTs) requiring evaluation of clinical validity and utility[15]. International regulatory standards remain inconsistent[15].

2. Feasibility Considerations: Sampling Intervals and Clinical Implementation

2.1 Defining Appropriate Surveillance Intervals

A fundamental question for WES-based chemoprevention assessment is: how frequently should individuals undergo genomic reassessment and clinical surveillance? This question intersects multiple domains: genomic stability, biological behavior of precancerous lesions, chemoprevention efficacy, patient tolerance, and healthcare system capacity[16].

Biological Basis for Interval Selection: Cancer development typically involves accumulation of multiple genetic alterations over years or decades. For chemoprevention applications, surveillance intervals should be informed by: (1) natural history of cancer precursor lesions in individuals with specific genetic risk profiles; (2) expected timeline for chemoprevention agent effects; (3) data on progression rates from precancer to invasive disease in the specific genetic context being studied[16].

For colorectal cancer prevention, this question has received substantial recent attention. Research employed polygenic risk scores (PRS) combined with colonoscopy findings to individualize surveillance intervals for colorectal cancer[16]. Leveraging data from 14,069 individuals in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), the authors constructed risk models incorporating: baseline risk factors (age, sex); 19 lifestyle and environmental factors; and a 455,995-SNP PRS derived from genome-wide association studies[16].

Challenges in Interval Selection:

1. Limited Natural History Data: For many cancers and specific genetic variants, longitudinal natural history data remain sparse, making evidence-based interval selection difficult[17].

2. Population Heterogeneity: Optimal intervals likely differ substantially based on: specific germline variant profiles; environmental exposures; chemoprevention adherence; and prior surveillance findings[17].

3. Cascade Versus Index Stratification: First-degree relatives of individuals carrying pathogenic variants (cascade testing candidates) may require different surveillance intervals than index probands based on different prior exposures and healthcare engagement[17].

2.2 Infrastructure Requirements and Workflow Integration

Successful implementation of WES-based chemoprevention programs requires substantial infrastructure investment spanning multiple domains[18]:

Sequencing and Laboratory Capacity:

- High-throughput DNA sequencing platforms capable of processing 50–1000+ samples simultaneously
- Standardized sample collection, storage, and tracking systems
- Quality control protocols ensuring ≥99.9% variant calling accuracy, particularly for clinical reporting
- Capacity for ~500–1000× average coverage depth to maximize variant detection sensitivity[18]

Bioinformatic Infrastructure:

- Automated pipelines for read alignment, variant calling, and annotation
- Integration of databases containing pathogenic variant information (ClinVar, HGMD, cancer-specific databases)
- Machine learning models for predicting variant pathogenicity when clinical data are limited
- Capacity for periodic database updates reflecting newly-published variant interpretations[18]

Clinical Integration:

- Genetic counseling services for both pre- and post-test counseling
- Medical decision support systems integrating WES results with clinical risk models
- Electronic health record (EHR) interfaces for result reporting and clinical annotation
- Population health surveillance systems tracking screening completion and chemoprevention adherence[18]

Workforce Development:

- Adequately trained genetic counselors (critically short supply in many regions)
- Oncologists and primary care physicians skilled in interpreting and acting on genomic risk information
- Laboratory directors and bioinformaticians capable of maintaining quality standards[18]

2.3 Turnaround Times and Clinical Workflow

Rapid turnaround time from sample collection to result report and clinical counseling is essential for chemoprevention programs targeting acute clinical moments (e.g., breast surgery assessment, colorectal polyp removal)[19]. Current WES turnaround times typically range from 10–30 days for single samples, depending on laboratory volume and complexity of interpretation[19]. For context[19]:

- DNA extraction and sequencing: 1–3 days
- Initial bioinformatic analysis and variant calling: 2–5 days
- Variant annotation and clinical interpretation: 3–7 days (highly variable depending on clinical complexity and availability of genetic counselors)
- Report generation, review, and physician communication: 2–3 days

These timelines can be compressed in high-volume laboratories, but interpretation complexity (particularly managing incidental findings see Section 3) often creates bottlenecks. For cancer prevention applications where urgency is generally lower than in acute cancer diagnosis, this timeline may be acceptable, but it introduces delays in conveying results to patients and initiating counseling[19].

2.4 Sampling Procedures and Sample Quality

WES for germline cancer risk assessment typically utilizes DNA from peripheral blood or saliva, both minimally invasive collection modalities well-suited to prevention programs[20]. However, sample quality issues can introduce false negatives and false positives:

Blood-derived DNA:

- Advantages: Established protocols, high DNA yield, high purity standards for clinical testing[20]
- Challenges: Requires phlebotomy (minor discomfort, anxiety in some patients), sample degradation if not properly processed, potential for sample tracking errors in high-volume settings[20]

Saliva-derived DNA:

- Advantages: Non-invasive collection, easier at-home self-collection, reduced sample tracking risk[20]
- Challenges: Lower DNA concentration and purity compared to blood, potential for bacterial contamination affecting sequencing quality, variable DNA yield between individuals[20]

Recent evidence suggests that properly processed saliva samples yield DNA adequate for WES with quality parameters equivalent to or exceeding blood samples[20]. This has implications for population-scale chemoprevention programs where at-home saliva collection could substantially expand access and reduce collection site infrastructure requirements[20].

3. Ethical Framework for WES in Preventive Genomics

3.1 Foundational Ethical Principles and Challenges

WES-guided cancer chemoprevention raises complex ethical questions not fully addressed by existing frameworks developed for diagnostic genetic testing or therapeutics[21]. Key ethical tensions include[21]:

Autonomy vs. Beneficence: WES results generate numerous incidental findings variants unrelated to cancer susceptibility but potentially disease-relevant creating tension between respect for patient autonomy (allowing individuals to choose which results they receive) and beneficence (ensuring individuals receive information enabling health optimization)[21].

Individual vs. Family Implications: Germline variants with implications for chemoprevention choice affect not only the tested individual but also first-degree relatives through cascade testing, introducing questions about obligations to disclose family-relevant information and family decision-making authority[21].

Prevention vs. Treatment: Chemoprevention involves administering pharmacological agents to individuals currently without cancer, raising different ethical considerations than cancer treatment (where immediate benefit justifies greater risk acceptance)[21].

Uncertainty Management: Many variants identified through WES have uncertain clinical significance neither clearly pathogenic nor clearly benign raising questions about communicating uncertainty to patients and managing their psychological burden[21].

3.2 Informed Consent in Preventive Genomics

Informed consent for WES-based chemoprevention assessment must address several elements beyond standard genetic testing consent[22]:

Scope and Potential Findings:

- Clear communication regarding what WES measures (germline cancer variants, pharmacogenomic variants, incidental findings)
- Explanation of variant categories (high-penetrance, moderate-penetrance, polygenic risk scores, variants of uncertain significance)
- Specific discussion of likely incidental findings: approximately 1–3% of WES participants carry pathogenic variants in medically actionable genes unrelated to cancer[22]

Limits of Knowledge:

- Honest communication regarding: gaps in knowledge about cancer risk associated with specific variants; insufficient data on chemoprevention efficacy for rare variants; uncertainties regarding interpretation of polygenic risk scores across diverse populations[22]
- Discussion of variant reclassification the likelihood that currently benign variants may be reclassified as pathogenic as evidence accumulates[22]

Return of Results Policies:

- Explicit discussion of which variants will be reported versus which will not
- Clarity regarding timing and format of result communication
- Discussion of cascade testing implications and obligation (if any) to inform relatives[22]

Psychological and Social Implications:

- Potential psychological burden of learning about elevated cancer risk
- Possible implications for employment, insurance, and life planning
- Strategies for managing genetic anxiety[22]

Recent evidence suggests that existing informed consent processes for genomic testing often inadequately address these elements[22]. Studies examining consent documents from commercial genetic testing labs frequently found insufficient information regarding: incidental findings (addressed in <50% of consent forms), variant reclassification (addressed in ~25%), and pharmacogenomic information (~15%)[22].

3.3 Incidental Findings Management

When WES is performed for cancer risk assessment, systematic analysis of the exome frequently identifies pathogenic variants in medically actionable genes unrelated to cancer susceptibility[23]. American College of Medical Genetics (ACMG) guidance recommends return of incidental findings in 59 medically actionable genes, including BRCA1/BRCA2, Lynch syndrome mismatch repair genes, familial hypercholesterolemia genes (LDLR, PCSK9, APOB), cardiac risk genes (TNNI3, HCM genes), and sudden cardiac death susceptibility genes[23].

Ethical Dilemmas in Incidental Finding Management:

1. Autonomy and Right Not to Know: Patients have an ethical right to decide whether to receive incidental findings unrelated to their indication for testing[23]. However, implementing this right requires: identifying patients' preferences prospectively (often impractical), managing situations where patients change preferences, and navigating situations where incidental findings have immediate health implications[23].

2. Secondary Finding Selection: ACMG criteria specify 59 genes for return; however, >50% of WES participants carry at least one non-medically actionable variant of potential clinical significance in non-ACMG genes (e.g., possible moderate-penetrance disease variants)[23]. Determining which additional variants to report introduces subjective value judgments about health importance and clinical actionability[23].

3. Variant of Uncertain Significance (VUS): Approximately 10–15% of clinically interpreted variants receive "uncertain significance" classifications, with unclear guidance on whether these should be returned to patients[23].

Proposed Framework for Incidental Findings Return:

Recent guidelines recommend[23]:

- Opt-in approach (preferred): Allow patients prospectively to indicate whether they wish to receive secondary findings, with reasonable default of non-return
- Tiered reporting: Distinguish between high-confidence, medically actionable findings (ACMG-defined genes) versus uncertain or less actionable findings
- Genetic counseling: Provide pre- and post-result counseling for all clinically significant incidental findings
- Regular reassessment: Allow patients to update preferences regarding incidental finding return periodically (e.g., annually)

3.4 Genetic Discrimination and Privacy Concerns

Despite protections like the Genetic Information Nondiscrimination Act (GINA, U.S., 2008) and similar legislation in other countries, concerns regarding genetic discrimination persist as documented barriers to genomic testing uptake, particularly in vulnerable populations[24].

Insurance and Employment Discrimination:

GINA prohibits use of genetic information in health insurance and employment decisions; however[24]:

- GINA applies only to group health insurance and employers with ≥15 employees leaving gaps for self-employed individuals, small business employees, and individual insurance markets
- GINA does not cover life insurance, disability insurance, or long-term care insurance contexts where genetic information may be highly relevant[24]
- Data suggest employers continue to request genetic information informally in some contexts, despite legal prohibitions[24]

Psychological Effects of Discrimination Concerns:

Surveys indicate that 22–35% of individuals offered genetic testing for cancer susceptibility decline testing primarily due to fears of discrimination despite legal protections[24]. This represents a significant equity issue: individuals already experiencing structural marginalization (poverty, immigration status, racial/ethnic minorities) express higher discrimination concerns and lower testing acceptance rates[24].

Recommended Protective Strategies:

1. Enhanced Legal Protections: Advocacy for extending GINA coverage to additional insurance types and addressing international variations in genetic discrimination law
2. Education and Public Communication: Targeted education regarding existing legal protections and actual (versus perceived) discrimination risks
3. Data Security Enhancement: Implementing robust cybersecurity protocols and regulatory oversight of genomic data storage and sharing
4. Transparent Governance: Establishing clear policies regarding secondary use of genomic data for research, marketing, or law enforcement applications[24]

3.5 Equity and Justice in WES-Based Cancer Prevention

WES-based chemoprevention assessment risks exacerbating existing cancer disparities if implementation is inequitable[25]:

Population-Level Implications:

- Ancestry-Based Performance Variation: Polygenic risk scores derived primarily from European ancestry populations show substantially reduced predictive accuracy when applied to individuals of African, East Asian, or Hispanic ancestry creating risk of differential risk stratification by race/ethnicity[25]
- Limited Diversity in Genomic Reference Data: Approximately 80% of GWAS data derive from European ancestry individuals despite Europeans representing only ~15% of global population. This creates systematic bias in variant interpretation, frequency estimation, and polygenic risk score construction[25]
- Chemoprevention Efficacy Variation: Many randomized trials of chemoprevention agents have underrepresented non-European populations, limiting evidence regarding efficacy across diverse populations[25]

Structural Barriers to Equitable Implementation:

Even if WES were equally accurate across populations, implementation barriers would likely perpetuate disparities[25]:

- Genetic counseling expertise concentrated in academic medical centers with limited access for rural or low-income populations
- Language barriers in providing genetic counseling and informed consent to non-English-speaking populations
- Limited insurance coverage for genetic testing and counseling in safety-net healthcare systems
- Lower baseline healthcare engagement and trust in prevention services among historically marginalized populations[25]

Recommended Approaches to Advancing Equity:

- Research Diversity: Increased funding for genomic research in non-European populations to enable accurate ancestral adjustment of risk scores and variant interpretation
- Integrated Care Models: Embedding genetic counseling and chemoprevention within primary care and specialty care rather than referring to specialized genetic clinics
- Community-Based Implementation: Partnering with community health workers and trusted community organizations to deliver genetic testing and counseling services
- Literacy-Appropriate Communication: Developing simplified, literacy-appropriate educational materials and utilizing visual aids to communicate genomic risk concepts[25]

4. Regulatory Framework and Professional Society Guidance

4.1 FDA Regulation of WES-Based Testing

FDA regulatory oversight of WES has evolved substantially over the past decade, reflecting the technology's transition from research tool to clinical testing modality[26]:

Classification and Regulatory Pathway:

The FDA classifies WES-based tests as either[26]:

1. Companion Diagnostics (if linked to specific chemoprevention agents): Require premarket approval or 510(k) clearance based on clinical evidence demonstrating the test's performance characteristics and clinical utility for the specific therapeutic context

2. Laboratory-Developed Tests (LDTs): Tests developed and offered by individual laboratories without prior FDA review, historically under Clinical Laboratory Improvement Amendments (CLIA) oversight. However, recent FDA initiatives have moved toward requiring premarket validation for clinically significant LDTs[26]

Recent Regulatory Developments:

In 2023, the FDA announced a proposed rule requiring premarket review of LDTs classified as high-risk or moderate-risk a category potentially encompassing WES-based cancer risk assessment tests[26]. The rationale included: documented quality variations among LDT providers, inadequate clinical validity evidence for some marketed tests, and consumer protection considerations[26].

Clinical Validity and Utility Requirements:

For WES-based cancer prevention tests, FDA expects demonstration of[26]:

1. Analytical Validity: ≥99.9% accuracy in variant calling and classification, demonstrated through comparison to gold-standard reference samples. For clinically significant variants, this translates to <1 false positive or false negative per 1,000 variants[26]

2. Clinical Validity: Demonstrated association between identified variants and cancer risk, typically quantified through odds ratios or hazard ratios derived from peer-reviewed literature or prospective cohort studies. For rare pathogenic variants, this may rely on established databases (ClinVar, HGMD) and expert curated evidence[26]

3. Clinical Utility: Evidence that testing results inform clinical decisions and lead to improved health outcomes. For chemoprevention applications, this requires demonstrating: (1) differential chemoprevention recommendations based on test results; (2) acceptable chemoprevention side effect profiles in the tested population; (3) measurable reduction in cancer incidence or improved quality-adjusted life years[26]

4.2 International Regulatory Perspectives

Regulatory frameworks for genomic testing in cancer prevention vary substantially internationally, reflecting differing healthcare systems and policy priorities[27]:

European Union:

- In vitro Diagnostic Regulation (IVDR) effective 2022 requires premarket performance and clinical validity evidence for all in vitro diagnostic devices
- European Medicines Agency (EMA) provides guidance on pharmacogenomic test requirements for drugs in development
- European Society of Human Genetics (ESHG) publishes detailed guidelines for best practice in genomic testing, including recommendations for bioinformatic pipelines, quality standards, and result reporting[27]

United Kingdom:

- All National Health Service (NHS) genomic testing is centralized through seven Regional Genomic Laboratory Hubs, enabling consistent quality standards and equitable access

- NHS England has published specific guidance on implementing genomic medicine in cancer care, including recommendations for chemoprevention assessment[27]

Canada:

- Provincial health systems regulate genomic testing through laboratory licensing and quality standards
- Canadian Association of Genetic Counsellors provides professional guidelines for practice standards[27]

Australia:

- National Pathology Accreditation Advisory Council (NPAAC) sets standards for genetic testing laboratories
- Cancer Council Australia has published guidance on genomic testing in cancer prevention[27]

4.3 Professional Society Recommendations

Major oncology and genetics professional societies have published or are developing guidance on genomic testing utilization in cancer prevention[28]:

American Society of Clinical Oncology (ASCO):

ASCO recommends that chemoprevention eligibility determination incorporate: risk stratification using established models, individualized assessment of benefit/risk (considering comorbidities, patient values, baseline cancer risk), and discussion of preventive options including lifestyle modification, surveillance, and pharmacological chemoprevention[28].

While ASCO has not published specific guidance on WES utilization in chemoprevention, the Society has emphasized the importance of: (1) clinical validity and utility evidence before implementing genomic testing; (2) equitable access to testing and interpretation services; (3) integration with genetic counseling; and (4) prospective patient consent regarding incidental findings[28].

National Comprehensive Cancer Network (NCCN):

NCCN guidelines address genetic testing for hereditary cancer susceptibility but have not published specific chemoprevention assessment frameworks. However, NCCN recommends[28]:

- Genetic testing for pathogenic variants in high-penetrance genes (BRCA1/BRCA2, Lynch syndrome genes, etc.)
- Incorporation of family history assessment
- Consideration of ethnicity-specific testing (e.g., BRCA1/BRCA2 founder mutations in Ashkenazi Jewish populations)
- Multidisciplinary team approach including genetics, oncology, and risk assessment[28]

American Society of Human Genetics (ASHG):

ASHG policy statements address ethical issues in genomic research and clinical testing, including recommendations regarding[28]:

- Broad consent models that allow flexible return of results reflecting individual preferences
- Transparency regarding commercial use of genomic data
- Data sharing practices balancing research benefits against privacy risks
- Protection of research participants from discrimination[28]

4.4 Evidence Standards and Burden of Proof

A critical issue in regulatory frameworks concerns the burden of proof required before implementing WES-based chemoprevention assessment[29]:

Proposed Models:

1. Traditional Evidence-Based Model: Requires randomized controlled trials (RCTs) demonstrating that WES-guided chemoprevention reduces cancer incidence compared to standard risk assessment before regulatory approval or widespread implementation[29]

2. Evidence Generation in Real-World Settings: Allows WES implementation with concurrent prospective data collection to generate evidence regarding clinical utility. This model assumes insufficient RCT evidence may be available given long follow-up periods required for cancer incidence endpoints[29]

3. Risk-Based Regulatory Approach: Differentiates between low-risk test applications (e.g., identifying high-penetrance pathogenic variants with clear cancer associations) versus higher-risk applications (e.g., polygenic risk score interpretation for common variants in understudied populations). Lower-risk applications may proceed with less evidence while higher-risk applications require more rigorous validation[29]

Current regulatory trajectory in the U.S. and internationally appears to favor a hybrid model incorporating elements of both traditional evidence-based approaches and risk-stratified frameworks[29]. This is pragmatic but creates challenges: some WES applications with sufficient clinical validity and utility evidence may face implementation delays while awaiting RCT evidence, while other applications with lesser evidence may proceed to clinical implementation[29].

5. Cost-Effectiveness Analysis and Economic Evaluation

5.1 Technology Costs and Trend Analysis

WES costs have declined dramatically over the past decade, reflecting maturation of sequencing technology, competition among sequencing providers, and increasing throughput[30]:

Historical Cost Trajectory:

- 2010–2012: $3,000–5,000 per exome
- 2013–2015: $1,000–2,000 per exome
- 2016–2018: $500–1,000 per exome
- 2019–2021: $300–600 per exome
- 2022–2025: $200–500 per exome, with largest labs achieving $100–200 per sample at high volume[30]

Cost Components Breakdown (representative 2024 data from high-volume academic laboratory):

- DNA extraction: $5–10
- Library preparation and sequencing: $50–100
- Bioinformatic analysis and variant calling: $20–50
- Variant annotation and database integration: $10–20
- Report generation and physician review: $30–50
- Genetic counselor time (if included): $100–200
- Administrative overhead: $30–50
- Total cost to laboratory: $245–480
- Typical clinical billing: $500–2,000 (highly variable by institution and payer)[30]

Comparison with Alternative Testing Modalities:

- Targeted gene panel (10–50 genes): $200–600
- Whole genome sequencing (WGS): $400–1,500
- Sequential single-gene testing (BRCA1 + BRCA2): $500–2,000[30]

5.2 Chemoprevention Intervention Costs

Cost-effectiveness of WES-guided chemoprevention depends not only on testing costs but on costs of chemoprevention interventions and surveillance following risk stratification[31]:

Pharmacological Chemoprevention Costs (annual):

- Tamoxifen (breast cancer prevention): $50–200 (generic, highly variable by volume and region)
- Aromatase inhibitors (breast cancer prevention): $100–500
- Aspirin (colorectal cancer prevention): $20–100
- Finasteride (prostate cancer prevention): $50–150
- Novel targeted agents (for specific genetic contexts): $1,000–5,000+[31]

Associated Costs:

- Baseline assessment and risk stratification: $500–2,000 (includes clinical evaluation, genetic counseling)
- Periodic surveillance and monitoring: $500–2,000 annually (varies by chemoprevention agent and monitoring requirements)
- Management of adverse effects: $500–5,000+ (highly variable depending on chemoprevention toxicity profile)
- Psychological support and counseling: $100–500[31]

5.3 Cost-Effectiveness Evidence in Cancer Prevention

The evidence base for cost-effectiveness of genomic testing in cancer prevention remains limited and heterogeneous[32]:

Breast Cancer Prevention Context:

A notable gap exists in cost-effectiveness literature for WES-guided breast cancer chemoprevention. However, cost-effectiveness analyses of BRCA1/BRCA2 testing (a subset of what WES provides) generally demonstrate favorable economics[32]:

- Testing costs: $1,500–3,000 per individual
- Cost per cancer case prevented: $50,000–100,000 (highly dependent on mutation frequency in studied population, chemoprevention efficacy, and baseline cancer risk)[32]
- Most analyses suggest BRCA testing is cost-effective at willingness-to-pay thresholds of $100,000–150,000 per quality-adjusted life year (QALY)[32]

Colorectal Cancer Prevention Context:

Recent health economic analyses of WES-guided surveillance interval adjustments for colorectal cancer provide more direct evidence[32]:

The precision screening strategy analysis evaluated risk-stratification-based surveillance in esophageal cancer (related methodology applicable to colorectal cancer)[32]:

- Base case analysis: Precision strategies reduced average cost per severe dysplasia case detected from $14,944 (traditional strategy) to $7,148–11,537 (precision strategies) approximately 50% cost reduction

- Incremental cost-effectiveness ratios (ICER): Precision strategies achieved negative ICERs (-$54,666 to -$25,726 per case detected) when compared to traditional strategies, indicating both greater effectiveness and lower cost
- Sensitivity analysis: Across willingness-to-pay ranges from $9,465–60,478 per case detected, precision strategies remained preferred[32]

Limitations of Current Evidence:

Despite promising findings from colorectal cancer models, generalizing to broader WES-guided chemoprevention remains problematic[32]:

1. Heterogeneous Outcomes: Different cancer types show different natural histories, baseline incidence rates, chemoprevention efficacy, and cost structures limiting ability to generalize findings
2. Lack of RCT Evidence: Most cost-effectiveness analyses rely on observational data or modeling rather than prospective RCT evidence
3. Population Specificity: Cost-effectiveness varies substantially based on baseline cancer risk in studied population (enriched high-risk cohorts show different cost-effectiveness than general populations)
4. Uncertainty in Long-Term Outcomes: Most analyses project over 5–10 years; longer-term sustainability of chemoprevention adherence and cancer prevention effects remain uncertain[32]

5.4 Methodological Challenges in Evaluating Cost-Effectiveness

Several methodological complexities complicate cost-effectiveness assessment of WES in cancer prevention[33]:

Challenge 1: Multifactorial Nature of Cancer Risk:

Individual cancer risk depends on hundreds of genetic and environmental factors plus their interactions. Determining which portion of observed cancer risk reduction can be attributed to WES-guided intervention (versus other factors) is methodologically complex[33].

Challenge 2: Population Heterogeneity:

WES-driven cost-effectiveness differs dramatically based on population characteristics[33]:

- Enriched high-risk populations (e.g., breast cancer patients requesting preventive counseling, individuals with strong family history): WES may identify substantial genetic risk burden; high baseline cancer risk makes chemoprevention more cost-effective; testing yields more actionable findings → favorable cost-effectiveness
- General populations (e.g., routine cancer prevention screening): Lower baseline variant burden; chemoprevention impact on lower-baseline-risk individuals may not justify costs → potentially unfavorable cost-effectiveness
- Specific ancestry populations (e.g., Ashkenazi Jewish populations with higher BRCA prevalence; individuals of African ancestry with specific variant allele frequencies): Different variant frequencies create different risk profiles and different cost-effectiveness calculations[33]

Challenge 3: Time Horizon and Discount Rates:

Cancer prevention interventions may take years or decades to demonstrate health benefit, requiring cost-effectiveness analyses to project far into the future with inherent uncertainty. Discount rates (typically 3–5% annually) applied to future health benefits substantially affect cost-effectiveness ratios[33].

Challenge 4: Incorporating Patient Preferences and Values:

Traditional cost-effectiveness analysis focuses on clinician-determined objective health outcomes (cancer cases prevented, quality-adjusted life years). However, patients may value[33]:

- Peace of mind from knowing genetic risk status

- Psychological burden of learning about genetic susceptibility
- Lifestyle changes encouraged by chemoprevention programs
- Value of information enabling family-level prevention strategies

Incorporating these subjective values into cost-effectiveness frameworks remains methodologically challenging[33].

5.5 Healthcare System and Economic Context Effects

Cost-effectiveness of WES varies substantially depending on healthcare system structure and economic context[34]:

High-Income Countries with Universal Healthcare:

In systems like the UK NHS or Canadian provincial health systems, WES cost-effectiveness analysis may incorporate[34]:

- Lower negotiated WES costs due to centralized purchasing power
- Streamlined implementation through centralized testing facilities
- Better tracking of long-term outcomes through integrated EHR systems
- Universal access to chemoprevention agents, removing individual cost barriers

These features generally favor WES adoption at population scale[34].

High-Income Countries with Market-Based Healthcare (U.S. Model):

In fragmented U.S. healthcare system[34]:

- Higher WES costs due to competition-driven pricing variation
- Inconsistent insurance coverage and reimbursement
- Fragmented patient tracking and outcome measurement
- Individual cost barriers to chemoprevention access even if WES is covered
- Greater inequality in access based on insurance status and geography

These features create less favorable cost-effectiveness picture for broad implementation[34].

Low and Middle-Income Countries (LMICs):

WES implementation faces different economic considerations[34]:

- Resource constraints typically favor simpler, less expensive risk assessment approaches (family history, basic clinical assessment)
- Even low WES costs ($200–300) may represent substantial portion of annual healthcare spending per capita
- Limited access to genetic counseling, chemoprevention agents, and surveillance infrastructure
- Potential for greater impact in LMIC context given lower baseline cancer prevention infrastructure (WES could "leapfrog" older diagnostic approaches)

For LMICs, cost-effectiveness often depends on specific epidemiological context (e.g., would WES identify substantial BRCA1/BRCA2 burden in specific populations) and feasibility of linking genetic testing to accessible prevention interventions[34].

6. Integrated Implementation Framework

6.1 Patient Selection and Risk Stratification

Maximizing WES utility in cancer prevention requires thoughtful patient selection informed by[35]:

Appropriate Testing Indications:

1. High-Penetrance Pathogenic Variants: Strongest indication individuals with personal or family history suggestive of hereditary cancer syndrome
2. Polygenic Risk Scores in Enriched Populations: Moderate indication individuals with elevated baseline cancer risk (family history, prior precancerous lesions, specific occupational exposures)
3. Pharmacogenomic Stratification: Moderate indication when specific chemoprevention agents with known pharmacogenomic interactions are being considered
4. Population Screening: Weak indication general population screening lacks adequate cost-effectiveness evidence and may generate excessive incidental findings[35]

6.2 Genetic Counseling and Informed Consent

Effective implementation requires robust genetic counseling infrastructure addressing[35]:

Pre-Test Counseling Elements:

- Assessment of cancer risk based on personal and family history
- Explanation of WES methodology and interpretation limitations
- Discussion of test findings categories (pathogenic, likely pathogenic, variants of uncertain significance, benign)
- Transparent discussion of incidental findings: probability, types, decision-making regarding return of results
- Review of potential psychological, social, and family implications
- Assessment of patient understanding and readiness for testing[35]

Post-Test Counseling Elements:

- Detailed explanation of identified variants and cancer risk implications
- Discussion of chemoprevention options with benefits and limitations
- Exploration of lifestyle modification opportunities
- Family history assessment and cascade testing considerations
- Psychological support and connection to supportive resources
- Plans for longitudinal follow-up and surveillance[35]

6.3 Surveillance and Follow-Up Protocols

Implementing WES-guided chemoprevention requires clearly defined surveillance protocols including[36]:

Initial Risk Stratification:

- Integration of WES findings with clinical factors, family history, and environmental exposures to assign risk category (very low, low, moderate, high, very high risk)
- Selection of appropriate surveillance intervals informed by risk category [36]

Baseline Surveillance:

- Age-appropriate screening for the cancer type(s) in question
- Establishment of baseline imaging or endoscopic findings if relevant
- Assessment of chemoprevention eligibility and patient values[36]

Periodic Reassessment:

- Surveillance at intervals defined by risk category (e.g., 1–3 years for very high-risk individuals, 5–10 years for low-risk individuals)
- Incorporation of emerging risk factors or environmental exposures
- Opportunities for chemoprevention re-evaluation as new agents or evidence emerges
- Annual or biennial review of cascade testing recommendations for identified pathogenic variants[36]

6.4 Equity-Centered Implementation

Advancing equitable WES-guided chemoprevention requires specific implementation strategies[37]:

Workforce Development:

- Training genetic counselors, primary care physicians, and oncologists from underrepresented communities
- Provision of continuing education on equity issues in genomic medicine
- Establishment of career pathways for underrepresented genomics professionals[37]

Research Investment:

- Funding for diverse population genetic studies to reduce polygenic risk score disparity between European and non-European ancestry populations
- Chemoprevention efficacy studies explicitly examining efficacy across racial/ethnic groups
- Implementation science research examining barriers to equitable access to WES and chemoprevention[37]

Integrated Care Delivery:

- Embedding genetic counseling within primary care and specialty clinics rather than specialized genetics centers
- Community health worker training to deliver genetic literacy education and facilitate testing/counseling access
- Multilingual provision of educational materials and counseling services[37]

Transparent Communication:

- Clear communication regarding current limitations of genomic medicine across diverse populations
- Honest acknowledgment that WES performance may vary by ancestry
- Engagement of community stakeholders in shaping implementation priorities[37]

7. Future Directions and Emerging Opportunities

7.1 Technological Advances

Several technological developments promise to enhance WES utility in cancer prevention[38]:

Improved Variant Interpretation:

- Machine learning models predicting variant pathogenicity with greater accuracy
- Integration of functional genomics data (RNA-seq, proteomics) to assess functional impact of variants[38]

Polygenic Risk Score Enhancement:

- Multi-ancestry polygenic risk score development reducing performance disparities across populations
- Integration of gene-environment interactions into PRS models

- Development of dynamic PRS that incorporate evolving environmental and lifestyle factors[38]

Liquid Biopsy Integration:

- Cell-free DNA sequencing to detect somatic variants in blood of at-risk individuals, potentially identifying precancerous states before conventional detection
- Integration with germline WES to assess total cancer risk (germline + somatic burden)[38]

7.2 Evidence Generation Priorities

Critical research gaps requiring future investigation[39]:

Natural History Studies:

- Longitudinal prospective studies characterizing cancer development timelines in individuals with specific germline variants
- Particularly needed for variants of uncertain significance and uncommon moderate-penetrance variants

RCT Evidence:

- Randomized trials comparing WES-guided chemoprevention strategies versus conventional risk assessment
- Trials examining whether WES-informed risk stratification leads to improved health outcomes

Implementation Science Research:

- Pragmatic trials examining implementation strategies for equitable access to WES and chemoprevention
- Comparative effectiveness research examining different delivery models (centralized vs. decentralized, integrated vs. specialty)[39]

7.3 Integration with Other Prevention Modalities

Future cancer prevention programs likely will integrate multiple complementary approaches[40]:

Lifestyle and Environmental Interventions:

- Personalized lifestyle modification recommendations informed by genomic findings
- Integration of environmental exposure data with genetic risk assessment

Immunological Approaches:

- Development of cancer vaccines tailored to individual genomic profiles
- Integration with chemoprevention agents and surveillance strategies

Liquid Biopsy Surveillance:

- Use of blood-based biomarkers to assess early detection opportunities in high-risk individuals
- Dynamic risk reassessment based on somatic mutation detection[40]

Conclusion

Whole-exome sequencing (WES) holds significant promise for advancing cancer prevention by enabling precise risk stratification and more personalized chemoprevention strategies, but its clinical impact depends on overcoming substantial implementation challenges. Current evidence demonstrates that WES is technically feasible within prevention programs, although widespread adoption requires major investments in sequencing infrastructure, bioinformatics, genetic counseling, and clinical data integration, along with evidence-based determination of optimal sampling intervals that remain poorly defined for many cancers. Ethical considerations including management of incidental findings, informed consent under uncertainty, and persistent equity gaps due to variable performance of polygenic risk models across populations require more robust and standardized

frameworks. Regulatory oversight is evolving, particularly for laboratory-developed tests, yet guidance specific to WES-guided chemoprevention remains limited. While WES-informed risk stratification may be cost-effective in selected high-risk populations, broader applicability across diverse healthcare systems and ancestries is uncertain. Successful implementation will depend on standardized risk protocols, integrated counseling, transparent consent processes, equity-focused deployment, and continued prospective evidence generation.

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