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CONFRONTING THE "GRAY ZONES" OF TECHNOLOGY ASSESSMENT: EVALUATING GENETIC TESTING SERVICES FOR PUBLIC INSURANCE COVERAGE IN CANADA

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Abstract

We describe an evaluation model to guide public coverage of new predictive genetic tests in Ontario, Canada. The model confronts common "gray zones" in evaluation and coverage policy for challenging new technologies. Analysis addresses three domains of the evaluation picture. The first specifies evaluative criteria (purpose, effectiveness, additional effects, unit cost, demand, cost-effectiveness). The second induces or deduces acceptable cutoffs for each criterion. The third domain addresses the need to make decisions under uncertainty and to respond to "gray" evaluations with conditional-coverage decisions. The evaluation criteria should be applied within sound decision-making processes.

Keywords: Decision making, Organizational, Health priorities/*organization & administration, Technology assessment, Biomedical /*organization & administration, Health care rationing, Genetics/legislation & jurisprudence

> "In the next decade, we will be able to do a lot of things.
> The question will be whether we should do them or not."
>
> L. William Luria, M.D. on genetic testing, quoted in (29)

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New genetic diagnostics and therapeutics pose unprecedented challenges to the clinical practice, organization, and economics of modern health care systems. Genetic predictive tests are now available for hundreds of inherited conditions. Associations between testable genetic markers and population health are currently tenuous (5;6;7;48). Nevertheless, these tests have captured the attention of consumers and health care providers, and demand grows (10;21;30;39;55). Although genetic tests are valuable for the management of certain rare diseases (e.g., Huntington's disease), they offer mixed promise for the prediction and control of more common diseases (e.g., Alzheimer's disease) (32). Nonmedical uses such as family planning and actuarial risk profiling raise ethical concerns (60;91). Genetic tests' relatively high unit cost coupled with popular demand and commercial marketing create economic pressures for payers. Private, direct-to-consumer marketing is emerging (8;22;31;66). U.S. insurers inconsistently cover new genetic tests, depending on demand, unit costs, and expert consensus on clinical value (57;81). Advisory initiatives in Canada, the United States, and the United Kingdom are developing guidelines for the appraisal of genetic tests. Some serve regulatory approval decisions (2;3;28;50;51;64;72;82;89). Others support coverage and service planning decisions (22;38;53). Most of these guidelines remain works in progress. All rely on basic principles of technology assessment and evidence-based decision making, and require new tests to demonstrate their value empirically before acceptance as insured services.

This study introduces a "three-domain model" for technology assessment and coverage decision making regarding emerging genetic testing services. This model was developed to guide an Ontario (Canada) Advisory Committee's proposed evaluation framework (73). The model may be useful to other jurisdictions deliberating coverage of new predictive genetic tests. It is also potentially applicable to evaluating other health technologies with socially, medically, and economically challenging features.

Ideally, each new technology would exhibit "black-or-white "value that qualifies it for coverage (or not). Technology assessment would help paint this "black-and-white" picture. However, in policy practice (as in clinical practice [69]) many cases remain "gray" because several endemic problems muddy evaluation. First, some new technologies have new purposes (as well as effects) that are disorienting. For example, genetic tests can provide personally and socially relevant information about reproductive outcomes, paternity, or actuarial risk. A second source of gray is unclear standards regarding "how good is good enough" in terms of effectiveness, efficiency, and other evaluative criteria to merit coverage by public health insurance. Performance standards may be underdeveloped for health services in general, or stakeholders may dispute them for genetic tests in particular. Even with benchmarks in place, a third hue of gray appears in the form of missing, ambiguous, or incomplete evaluation information. Distinctive among barriers to good information is a fourth kind of gray: the blur of rapidly evolving technology and delivery contexts that alter a technology's purposes, effects, and costs after coverage decisions have been made. The following evaluation model confronts these "gray zones" and offers three vehicles for successfully navigating through them: (1) evaluation criteria, (2) acceptable cutoffs, and (3) conditions of coverage. Each of these three domains of analysis clarifies particular "gray" areas of policy making.

THREE-DOMAIN MODEL FOR EVALUATION

Domain One: Criteria

Many assessment-based models have been proposed for making health technology coverage decisions (12;18;19;25;26;33;40;67;68;74;86;87;92). Hurley et al. review many algorithms promoted internationally and conclude that "[diverse jurisdictions] consistently

argue that to be eligible for public funding a health care service must be demonstrated from a broader community or social perspective to be effective, efficient, necessary, and consistent with prevailing values in society"(52, p.9). A new generation of process-oriented (rather than criteria-oriented) models for coverage decision making has also appeared (24;44;83). Widely endorsed processes include, for example, accountability to citizens and stakeholders, explicitness in decision making, public participation, and assuming the perspective of "society" rather than individuals (24;44;52;83). Whatever the process, decision makers inevitably invoke and apply evaluative criteria to judge a new health service worthy of coverage. Thus, criteria-driven models remain important, within the context of fair process.

From the criteria-driven priority setting literature and its critiques (34;52;88), Table 1 distills basic questions of effectiveness, efficiency, normative issues, and technological assembly. Coverage criteria models nearly universally emphasize the importance of *effectiveness and efficiency* (or cost-effectiveness). Many *invoke normative criteria* as concerns separate from utilitarian effectiveness and efficiency (e.g., ethicality, social impacts, or individual or community preferences). To answer questions regarding effectiveness, efficiency, or ethicality, evaluators require a clear picture of a technology's purposes and functions, from a social as well as clinical perspective. These impacts may be complex, and not all stakeholders may view them the same way. "*Assembly*" questions critique the purposes, interests, and tradeoffs that characterize a given technology within its health system context (34). Questions such as "What is this technology for?" and, "How is it situated?" must precede questions of effectiveness, efficiency, and normative evaluation.

Advisory bodies have identified special evaluative issues germane to genetic tests (1–3;28;38;50;51;53;64;72;82;89). *Effectiveness* in the case of genetic tests involves at least three layers: (1) the ability of a test to detect the genetic sequence it seeks ("analytic validity"), (2) the association of the particular sequence with physiological defects or disease ("clinical validity"), and (3) the consequence of the genetic information for health outcomes ("clinical utility"). Social impacts must be anticipated and managed; these impacts include effects on relatives and progeny, informed consent by all affected, individual privacy, self-perception, and social attitudes (including discrimination, stigmatization, or protection of the vulnerable). *Resource allocation* dilemmas arise concerning opportunity costs, cost-effectiveness, and organizational feasibility of providing test services. *Demand* issues include the importance of certain genetic tests to population health needs, the burdens of genetically implicated diseases, and appropriate access to tests that become available.

We have distilled six basic criteria (Figure 1A–F) from these literatures. The criteria apply generically to any emerging health service, but our focus here is on adapting them to the assessment of genetic tests. Importantly, the unit of analysis to which the criteria apply is not just the laboratory test. Rather, what must be assessed for coverage is the *testing service*: the laboratory technology, plus a target population, plus a clinical context. The latter includes clinical objectives (e.g., screening, prediction, diagnosis, treatment planning) and routes of access (e.g., private market, on demand, by referral). For evaluation and the coverage decision to be meaningful, each of these three elements must be specified, and the service considered as a whole. Once the service is defined, assessment proceeds through criteria A-F (Figure 1) to determine its merit for public insurance coverage.

Criterion A: Intended purpose. A technology's specified purpose provides fundamental orientation to assessment and policy decisions. As "there is nothing so useless as doing efficiently that which should not be done at all"(27), the description and evaluation of purpose should precede evaluation of effectiveness and cost-effectiveness. Much current discomfort about covering genetic tests arises from their manifold and sometimes novel purposes. Advocates and skeptics may disagree over the essential purpose of a new genetic test or the genetic testing enterprise altogether. To guide assessment, a testing service's intended

Table 1. General criteria for the evaluation of health technologies

Effectiveness and Efficiency Questions

- ***Does the technology work?***
  - Is empirical evidence available regarding the technology's effectiveness?
  - How well does evidence of effectiveness comply with clinical epidemiology principles for critical appraisal?
  - Does the technology work well enough? Compared to what?
- ***Is it cost effective?***
  - Is the technology cost-effective? Compared to what? For what purpose?
  - How much does the technology cost, and how effective is it?
  - What is the distribution of its costs and benefits across members of society? Who pays the costs? Who enjoys the benefits?

Normative Questions

- ***Do individuals want it?***
  - How important are personal preferences and principles of autonomy in valuing the technology?
  - What economics and institutions influence these personal preferences (e.g., marketing, culture, clinicians)?
  - What social relationships influence personal preferences (e.g., relatives with a stake in te genetic information)?
- ***Does the community want it on behalf of individuals?***
  - How important are principles of solidarity, compassion, etc., in valuing the technology?
  - Does the community have a direct interest in offering this technology to individuals (i.e., due to externalities)?
  - Have individuals been granted legal entitlements or rights to this technology (i.e., by legal precedent or legislation)?
- ***Is it equitable to cover this technology at the expense of other things?***
  - Are the costs and benefits of coverage shared fairly (not equally, but equitably) across members of society?
- ***Is the technology otherwise ethical?***
  - Many other ethical principles may come into play, e.g.: human rights, dignity, reproductive rights, discrimination, privacy, and so forth.

Assembly Questions

- ***What is the technology and what is it for?***
  - Why address this technology (e.g., "new" genetic tests) as distinct from other health technologies (e.g., conventional genetic diagnostics)?
  - What features define this technology and its subtypes?
  - Should the technology be defined narrowly (e.g., lab test) or broadly (e.g., all necessary services to accomplish a clinical aim)?
  - Is its purpose to produce wellbeing, health, mental health, physical health, knowledge, or something else?
  - What are the technology's potential effects *beside*s its intended purposes?
- ***How is it situated?***
  - Which other technologies does this technology entail (e.g., interventions subsequent to diagnosis, genetic counseling, etc.)?
  - Which existing technologies does this technology displace or otherwise affect?
  - What are this technology's alternatives (as suggested by its various purposes, above)?
- ***Whose is it, and who is it for?***
  - Which stakeholders are interested in this technology – for benefit, for profit, for information, etc.?
  - What are the political, economic, social relations between these stakeholders?
  - For which subpopulations *can* the technology currently work well?
  - Ideally, for which subpopulations *should* such technology work well?

purpose is its commendation by its advocates (i.e., a clear argument for what it is supposed to do and why this contributes to health care). Questions of effectiveness, "side" effects, costs, and so forth are not part of this criterion. Services with a *worthwhile* purpose merit further evaluation and consideration for coverage. Services with a purpose deemed *not-worthwhile*

	Criteria:	Standards for deciding coverage: Yes	No	Conditionally	Coverage conditions (if in "gray" zones):
Health impacts	A) Intended purpose	Clear and Worthwhile	Clear and Not worthwhile	Unclear	• Clarify before further evaluation or coverage decision
	B) Effectiveness	Known and Effective	Known and Ineffective	Unknown	• Research protocols (clinical evaluation)
	C) Additional effects	Known and Acceptable	Known and Unacceptable	Unknown or Worrisome	• Interventions • Ethics protocols • Regulatory oversight • Research protocols (descriptive & evaluative) • Clinical practice protocols
Economic impacts	D) Aggregate costs	n/a	Unaffordable	Potentially affordable	• Priority setting • Research protocols (economic evaluation)
	E) Demand	Stable	n/a	Growing	• Clinical practice protocols • Periodic re-evaluation
	F) Cost effectiveness	Known and Acceptable	Known and Unacceptable	Unknown or Unstable	• Research protocols (economic evaluation) • Periodic re-evaluation

Figure 1. Criteria, coverage conditions, and cutoffs for evaluating a new genetic test service for funding coverage.

should neither be covered nor evaluated further. If the purpose is *unclear*, it should be clarified and assessed before proceeding with evaluation or coverage decision making.

Criterion B: Effectiveness. Effectiveness refers to how well a technology accomplishes its purpose. For genetic tests, this is expressed in terms of clinical utility, which is a function of several nested features: (1) the availability and effectiveness of clinical interventions (e.g., surveillance or therapy); (2) the value of genetic information to the person or family tested, (3) the role and effectiveness of alternative (or supplementary) ways to assess risk, or to diagnose, understand, cope with, intervene into a genetic disease; (4) clinical validity–the performance of the test in terms of its sensitivity and specificity in detecting the genetic disease (and the quality of the evidence upon which such performance characteristics were derived), and, (5) analytic validity–the sensitivity and specificity of the test's detection of the analyte. Biomedical, personal, and social effects may be salient, and the assessment of additional effects (the criterion discussed next, below) should proceed in parallel with the assessment of effectiveness. The "bottom line" of an effectiveness assessment, however, is the extent to which the service does what it is supposed to do–whether it serves its purpose. *Ineffective* services should not be covered or evaluated further. Worthwhile and *effective* services warrant further evaluation and coverage consideration. Worthwhile services of *unknown* effectiveness might be covered under the condition that they are practiced under research protocols that will yield evidence of an acceptable degree of effectiveness.

Criterion C: Additional effects. Many genetic services have effects beyond their intended purpose or beyond the individual recipient of the test. We call "additional effects" any effects that are not adequately captured under the rubrics of "purpose" and "effectiveness," above. Such additional effects include personal or social effects beyond biomedical aims, the incidental discovery of unexpected problems, effects on others besides the person tested (family, progeny, etc.), and so forth. Opportunity costs are *not* a part of this assessment, as they are addressed later under the criterion of cost-effectiveness. Some additional effects (e.g., implications of genetic knowledge for untested family members) are shared by nearly all genetic tests, while other additional effects (e.g., side effects of subsequent interventions) may vary from test to test. If additional effects are well known and considered *acceptable*, a genetic testing service warrants further evaluation and consideration. If

additional effects are *unacceptable*, the service should not be covered. If additional effects for a compelling, effective service are *unknown or worrisome* for any reason, conditions may be placed on coverage. These conditions might include adequate interventions for the additional effects (e.g., counseling for family members). Depending on the effects, the genetic testing service may also receive extra oversight in the form of regulation, research study into additional effects that are poorly understood, or clinical practice protocols to ensure that additional effects are managed appropriately.

Criterion D: Aggregate costs. From the perspective of an insurer, the immediate, direct costs of covering a genetic test service at the population level is the product of the unit price and utilization (detailed methods for estimating costs and considering "downstream" costs are discussed elsewhere [41;65]). The unit price for evaluation should reflect all of the service elements that make the service's purpose worthwhile (Criterion A), its effectiveness adequate (Criterion B), and its additional effects acceptable (Criterion C). For example, these features might include multiple visits, an expert provider, certain laboratory protocols, counseling, etc. Utilization, or the quantity of services that would be provided, must be projected for the target population that defines the service. It depends on epidemiology as well as care-seeking behavior, opportunities, and constraints. From the perspective of the payer, the immediate, aggregate cost of the service may appear *unaffordable*. However, any judgement of affordability should be recast as *potentially affordable*, conditional on further evaluation of opportunity costs and cost-effectiveness.

Criterion E: Demand. Demand deserves evaluative scrutiny beyond its contributions to direct costs (criterion D, above) and cost-effectiveness (criterion F, below). Changes in demand can alter not only utilization and costs but also the essential definition of the genetic service by changing the target population. In doing so, changing demand patterns can invalidate original assessments of purpose, effectiveness, cost, etc. Several features of genetic testing tend to push demand beyond an original target population: commercial interests in expanding the market for proprietary tests, popular attitudes toward the importance of knowing one's genetic status (often regardless of familial or other risk indicators) (70;76), or improvements in preventive or therapeutic services subsequent to testing. For both economic and clinical reasons, it is important to assess the stability and growth potential of demand. If demand is limited and likely to remain *stable*, the "service" that is covered will better reflect the "service" originally evaluated for coverage. However, where demand is likely to grow beyond populations in whom the service's effects and effectiveness have been established, coverage might best be conditioned upon clinical practice protocols that limit access to appropriate groups. The purpose, effectiveness, and additional effects of the "new" service (i.e., defined in terms of new target populations) should also be re-evaluated periodically.

Criterion F: Cost-effectiveness. Cost-effectiveness evaluation estimates a service's resource requirements per unit yield (e.g., life years gained is a crude but common measure). Principles and methodological choices for evaluating the cost-effectiveness of genetic testing services are discussed elsewhere (37). The "costs" to be included in a cost-effectiveness estimate are more comprehensive than the immediate funding requirements referred to in criterion D (37;65). Cost-effectiveness does not equate, or even necessarily correlate, with expense to the health system. Inexpensive services of little effect have poor cost-effectiveness ratios; highly cost-effective services may nevertheless be unaffordable. Cost-effectiveness information is more uncertain and labile than either cost information or effectiveness information alone. It can change dramatically with changes in technology, target populations, the effectiveness of interventions subsequent to the genetic testing service, and so forth. Cost-effectiveness analysis aids utilitarian objectives (i.e., to maximize population benefits under a fixed budget). However, it seldom offers enough information to assess whether resources are thereby distributed equitably across subpopulations, stakeholders,

communities, etc. (80). An *acceptable* cost-effectiveness ratio for a genetic testing service will compare favorably with the ratios of other covered services, a benchmark, or an efficiency goal for the health system. *Unacceptable* cost-effectiveness indicates a service that yields too little for what it costs. If cost-effectiveness is *unknown*, decision makers concerned about cost-effectiveness may choose to cover the service on the condition that the service be provided under economic evaluation research protocols. If cost-effectiveness information is very uncertain or *unstable* due to imminent changes in technology, demand, or other factors, cost-effectiveness can be re-evaluated periodically. Good economic evaluation research often includes sensitivity analyses based on forecasts of likely changes in technology and other factors, but these may not represent actual changes in the clinical, technological, and funding environments, so re-evaluation remains important.

Domain Two: Cutoffs

"Cutoffs" are the coverage standards set for each evaluative criterion. Figure 1 displays jagged cutoffs between yes/no coverage decisions for all of the evaluation criteria outlined above. The jaggedness represents the negotiability of these lines. To apply an evaluative criterion in an accountable and consistent way, decision makers require a clear delineation of what is "good enough" from what is not. This value judgment is the crucial analytic step to make each criterion operational. The unit of analysis for this evaluative task is the *decision criterion* (not the genetic testing service). Table 2 lists (not exhaustively) some of the critical questions that analysts might have to answer for each criterion to transform it into an operational guide to decision making.

The process of developing these cutoffs may arise inductively out of the task of making specific coverage decisions about individual services tests. Alternatively, the two processes may be separated (i.e., one decision-making body defines the cutoffs in general, either inductively or deductively, then a subsequent body applies these standards to evaluate individual tests). Decision makers face several options for setting these cutoffs either deductively (deriving particular cutoffs from broader principles) or inductively (deriving the principles behind actual cutoffs from an examination of particular decisions).

Deduction from principles. Cutoffs could be derived deductively and in the abstract, in the absence of a given coverage case. For example, Laupacis et al. propose three classes of cost- effectiveness ratios in order of their acceptability: those costing $20,000 or less per quality adjusted life year, those $20,000-100,000, and those over $100,000 (58). Australia's public pharmaceutical coverage program implicity applies a cutoff of $78,000 per life year gained (43). Deductively derived cutoffs must invoke normative principles beyond the criteria included in the evaluation framework. This philosophically challenging project requires careful argument and justification. Citizens may supply guiding values by identifying principles or contributing to their operationalization (however, the many, and somewhat contentious, methods for involving public values are beyond the scope of this study).

Induction from pilot cases. Cutoffs can also emerge inductively through the deliberation of particular cases. Early decisions regarding the first genetic tests to be covered could set precedents to guide decisions about later tests. Because the first tests evaluated will structure subsequent evaluations, cutoffs may evolve differently from different pilot cases. Adherence to precedent requires good institutional memory, not only of the decisions made in the past but also of the reasons for making them. With qualitative investigation, intuitive rationales can be made explicit and formalized into principles (83); however, such investigations can also reveal prejudicial or inappropriate values guiding decisions (49).

Table 2. Sample analytic questions for defining the cutoffs for evaluative criteria

What will constitute a worthwhile purpose for a new health service?

- Are effects other than physical health (e.g., alleviation of anxiety, reduction of uncertainty, clarification of paternity, information for family or life planning, etc.) worthwhile goals *in themselves*? Or should they be valued strictly in terms of their physical health effects?
- Is generating intermediate clinical or biological information worthwhile in itself, or must testing results play a definitive role in diagnosis or treatment?
- If reduction of uncertainty (e.g., about one's carrier status) is a worthwhile goal, how much must a test reduce uncertainty to make it worthwhile?
- If life-saving is a worthwhile goal, how much life should be gained for a test to be worthwhile?
- If quality of life improvement is a worthwhile goal, how *much* improvement would be worthwhile, and according to what scale?
- etc.

What will constitute an effective health service?

- What would constitute scientifically adequate evidence of effectiveness?
- What are "important" effect sizes in each of the categories of worthwhile purpose, above?
- How should effects on others (externalities) be measured and assessed?
- How should harms offset benefits in the calculation of effectiveness? Could a particular harm trump all benefits, or is the judgment entirely a question of ratios and degrees?
- etc.

Which additional effects would be considered acceptable?

- Do genetic tests *as a class* present harms to societies or to groups within society? What are these? Does the degree of harm vary across specific types of tests, or according to a "critical mass" of genetic testing activity?
- Might certain genetic tests present any categorically unacceptable harms to societies or communities?
- If the benefits and burdens introduced by the service are not distributed equally through a population, what kinds of distributions would be adequately equitable?
- etc.

What is an acceptable level of costs for providing a new service?

- Considering the interactions between unit price, demand, and the potential for expanded demand consequent to coverage, how expensive (i.e., in terms of spending out of available budgets) is "too expensive"?

What is an acceptable level of cost effectiveness for a new service?

- How many units of effectiveness (e.g., life years gained, degrees of anxiety alleviated, etc.) per dollar of cost are required to qualify a new technology as a worthwhile investment?
- Whose interests should determine the parameters (time period, perspective, outcomes, etc.) of the cost effectiveness estimation?

Induction from precedents elsewhere in the health system. Cutoffs may be inductively generated from an examination of technologies already covered and well-accepted in the health system. One could argue that "grand-parented" technologies provide *de facto* standards by which to judge emerging technologies. Using this reasoning, for example, policy makers might cover a technology of low effectiveness if equally ineffective technologies already enjoy coverage. This approach pulls standards down to the lowest acceptable level and, thus, would fail to improve the quality of a health system that has not been purged of low-value technologies. To counteract this effect, decision makers might identify an exemplary technology within a class of covered technologies (e.g., screening tests, diagnostic tools, etc.) to serve as a "gold standard" for a given evaluation criterion. For example, to consider whether information-giving is a worthwhile purpose of a genetic test, decision makers might compare a new genetic test with a covered and uncontroversial test (perhaps, but not necessarily, another genetic test) with high information value.

Domain three: Conditions on coverage

Coverage decisions need not be "black and white" (i.e., "fund or not") but may come with conditions (i.e., "fund *when* . . . "). Our discussion of evaluation criteria (domain one) points to several coverage conditions that may be placed on genetic testing services of ambiguous or yet-unknown value. These conditions offer a way of covering promising services whose evaluations are indeterminate ("gray") for reasons that may change or that are highly dependent on context or behavior.

Indeterminate evaluations arise from several sources. First, services may fall on the cusp between acceptable and unacceptable categories. The clearer the cutoff standards (domain two), the fewer such cases will arise. Second, for any given criterion, the necessary evidence for evaluation may be missing or ambiguous. This is the reason that the column for "gray" cases in Figure 1 does not appear between the "white" and "black" categories: "gray" symbolizes not only "somewhere in between," but also "uncertain." Finally, features of the service itself (technology, epidemiology, demand, clinical context, etc.) may change rapidly–uncertainty arises from obsolescence as well as absence of information (41;65). Policy tools for placing conditions on coverage vary across jurisdictions and health systems. Figure 1 highlights several tools available in principle (if not in practice) in many health systems.

Clarification of purpose. Genetic testing services have many potential purposes, target populations, and roles in the clinical context. One test may do many things and may do them exceptionally well or poorly, depending on who exactly is served and what exactly is done before, during, and consequent to the test. Stakeholders knowledgeable about a service (and at least those who advocate its value for coverage, such as a biotechnology company or a patient interest group) must articulate exactly what the test is supposed to do, how, in which populations, and under which clinical contexts. If the definition of the testing service and its purpose cannot be described clearly, evaluation cannot proceed and coverage cannot be justified.

Research protocols. Research evidence is central to evaluation and coverage decision making, but assessment information may be uncertain or incomplete. When faced with the question of whether to cover promising but unsubstantiated reproductive technologies (e.g., in vitro fertilization), Canada's Royal Commission on New Reproductive Technologies in 1993 (78) recommended (albeit unsuccessfully [36]) that they be covered by public health insurance on the condition that care be provided only in the context of research protocols to generate better effectiveness data. It has been argued that anyone receiving an unproven health service is *de facto* a subject in an experiment and deserves the protection of research protocols requiring ethical treatment of human subjects (23;84). Similar options might be considered for genetic tests of compelling worth and promising, but yet unproven, effectiveness, or uncertain effects.

Periodic re-evaluation. New and evolving technologies are moving targets for assessment. Evidence on effectiveness, cost-effectiveness, and other criteria obsolesces quickly with changes in technology, target populations, disease interventions, and practice styles. The decision to cover a new testing service may significantly alter its value by changing demand and utilization patterns. For these reasons, genetic testing services may require periodic re-evaluation, and evaluations should model the effects of potential developments (e.g., changes in effectiveness, cost, target populations, clinical management) subsequent to the evaluation and coverage decision.

Interventions into personal and family impacts. Most genetic testing services include auxiliary interventions to control undesirable "side" effects of testing on individuals and their families. Thorough genetic counseling, for example, includes guidance on

how to deal with issues such as family members' interest in their genetic status, paternity questions, family planning, and so forth. Evaluators should identify such effects, and policy makers could condition coverage on servicing to ameliorate negative effects outside the scope of the testing service's main purpose. This strategy applies particularly to effects on the psychological and physical health of tested individuals and their families. For example, genetic counseling is widely considered a necessary adjunct service to genetic testing (13;14). Many health systems now strive to integrate multidisciplinary health services around patient needs, and genetic testing should follow this trend. Care components may be linked by features such as a single care site or well-managed care coordination (85). Equitable access to support services should be an aim of public as well as private funding structures (22).

Interventions into societal impacts. Genetic tests have potential social effects beyond impacts on the tested individual and relatives. Examples include cultural shifts in the meaning of health and risk, institutional changes in the practice of medicine, ownership and patenting disputes, and new forms of discrimination in insurance and labor markets (47;54;59;77). Social effects should be studied and understood as diligently as individual and family impacts. However, intervention is more challenging, and policy levers are typically beyond the direct reach of those deciding insurance coverage of individual tests. In the case of insurance discrimination, privacy and insurance reform legislation can address the problem (60;61). In the case of broader impacts on health and culture, scholars debate the merits of the genetic testing enterprise and industry altogether (5;48;62). Nevertheless, incremental coverage decisions contribute to the overall social impact of genetic testing (and genomics), and evaluators should keep abreast of the evolving scholarship in the legal and social sciences. Innovative policy making models (e.g., a national and widely representative commission devoted to the assessment, control, and provision of genetic technology [41;47;73]), may help orient disparate, "one-off" decisions toward a collective vision.

Clinical practice protocols. Clinical practice protocols include published practice guidelines as well as providers' unpublished, institutional protocols. Clinical guidelines have received much attention as public policy tools for reforming and rationalizing health care (9;11;15;35;42;71). Guidelines may be particularly appropriate where genetic testing practices vary substantially across providers (e.g., candidate screening, laboratory procedures), and these variations alter the service's value according to any of the six evaluative criteria. Clinical practice protocols can help control additional effects (by mandating interventions to mitigate these effects) or unreasonable growth in demand (by defining appropriate test candidates and restricting access). However, because providers' compliance with practice guidelines is voluntary, potential users must be persuaded of their value. Transparency about sources of evidence and the process of guideline development are two ways of strengthening content and acceptability (20;45;75;93).

Ethics protocols. Ethics protocols intervene into some of genetic testing services' potentially negative "additional effects." Conventional clinical ethics apply to genetic testing, but in many cases need interpretation and adaptation. Ethical protocols addressing topics such as consent, privacy, protection of research subjects clarify obligations of testing service providers (4;16;56;90). Advisory bodies have highlighted a rigorous consent process as a criterion for genetic test coverage (3;38). Less conventional ethical dilemmas arise from the complex and familial nature of genetic information. These dilemmas challenge policy makers to develop new ethical codes addressing consent and privacy (17;79).

Regulation. Formal legal regulation (as well as informal professional self-regulation) takes many forms; in Canada, dilemmas in genetic testing have generated a call for innovative

regulatory mechanisms at the federal and provincial levels (41;73). In the context of this evaluation framework, regulation serves two purposes. First, it can reinforce selected policy tools (clinical guidelines, adjunct interventions, mandatory research protocols, and protections, etc.) by legally requiring them. Norway for example has implemented legislation to control the practice of genetic testing services and require necessary adjunct services such as counseling (46). Many jurisdictions regulate laboratory standards and legally restrict the use of genetic information for nonmedical purposes (41;63;82). Second, regulations could ban genetic testing services whose impacts are harmful or unacceptable (e.g., as has been attempted with selected reproductive technologies in Canada and abroad). The enforcement of such regulations may be difficult where monitoring is poor or testing is accessed from foreign jurisdictions. Nevertheless, even toothless regulations can exert some moral suasion and influence both practices and demand (22).

Priority setting. Priority setting involves weighing the value of different health services funded within a defined budget and giving preference to some over others when resources are scarce. Many methods divine or develop these collective preferences to make fair choices among given options (for an overview, see reference 52). However, weighing options requires first identifying the appropriate "opportunity costs" of a given genetic testing service: if genetic testing receives more health care resources, *which* other service might possibly receive fewer? Opportunity costs are determined as much by the structure of funding and the politics of health resource structures as by the clinical purpose of a service (34). For example, depending on funding envelopes, the opportunity cost of a genetic test for hereditary breast cancer may be funding for *other genetic tests* (e.g., for Huntington's disease), funding for *other cancer services* (e.g., mammography, radiation therapy), funding for *general outpatient care* (e.g., everything else in the insurance plan fee schedule), or something else entirely. Priority setting choices depend not only upon the assessed value of an emerging technology but also upon how the service is paid for and how alternative investments are defined. Citizens and stakeholders may opine not only about the priority of a given genetic test but also which specific services to "prioritize" it against. Appropriate alternatives may differ from test to test.

Periodic re-evaluation. New and evolving technologies are moving targets for assessment. Evidence on effectiveness, cost-effectiveness, and other coverage criteria can become obsolete quickly. Changes in technology, target populations, disease interventions, practice styles and even coverage policies themselves may significantly alter a service's value (41;65). Because technology assessment takes time, evaluations may be outdated as they become available. For these reasons, genetic services will require periodic re-evaluation. Initial evaluations should also include sensitivity analyses based on developments and behavioral responses (e.g., changes in effectiveness, cost, target populations, clinical management) consequent to a coverage decision.

POLICY IMPLICATIONS

Resource allocation and coverage decisions require not only clear criteria, but systematic approaches to dealing with the ambiguity, uncertainty, and values that pervade "real world" decision making. We have developed a three-domain model to support decisions regarding the funding of new genetic testing services but applicable to a broader range of emerging health technologies. The model is structured around six widely endorsed criteria for judging the merits of health technologies for coverage. While evaluation of technological purpose has been left relatively implicit by most existing evaluation models (34;88), our model draws it into the fore. The three-domain model focuses on the "gray zones" of both evaluation and coverage decision making. It distinguishes among distinct areas of "gray," in particular:

- *Questionable objectives.* Technology assessment has well developed methods for assessing means (effectiveness, efficiency) but less systematic approaches to assessing ends (purposes). New medical technologies' purposes and effects must be judged for their moral, social, or political value before technology assessment information can inform decisions in a meaningful way.
- *Unclear cutoffs.* For each evaluative criterion, there is a gray area between "acceptable" and "unacceptable" classifications that needs to be clarified.
- *Missing information.* For any given evaluative criterion, there may be inadequate evidence to classify a given genetic testing service as "acceptable" or not according to the specified cutoffs.
- *Changing parameters.* Many new technologies evolve rapidly in service content (e.g., technology, technique, practice style, etc.) or delivery context (e.g., funding, demand, referral patterns, etc.). This "moving target" problem creates a distinctive type of information uncertainty, calling for distinctive remedies.
- *Conditional coverage.* When assessment determines that the value of a service is "gray," decision makers have the option of making a "gray" coverage decision in response. Specific coverage conditions correspond to specific "gray" qualities encountered in evaluation.

Reckoning with these "gray" zones will challenge several conventions of technology assessment and evidence-informed policy making. First, conventional discrimination between "experimental" and "proven" services is not very useful. Genetic diagnostics untested for human safety and efficacy are certainly "experimental" and unqualified for coverage in the absence of regulatory approval. However, the use of *approved* tests for expanded purposes, broadened populations, or within new delivery contexts is also "experimental." Private and public insurance coverage policies, commercial marketing, technological developments, and practice variations will foster the experimental use of once-proven technologies. For this reason, evaluation research should follow as well as precede insurance coverage. Data collection and analysis mechanisms are needed for monitoring and assessment of genetic testing services, and their sequelae, in practice.

Second, the case of genetic testing graphically reveals the web of connections between services in a health care system. The promise of genetic tests is entangled with the use and impact of many other technologies and practices. Technology assessment, therefore, must address programs of integrated genetic risk management services, not individual tests. If evidence is to inform "gray" conditional coverage policies, evaluation should account for variants of servicing models (e.g., different gatekeepers or providers), as well as the contributions of necessary components (e.g., counseling, testing, interventions, surveillance, etc.) to overall health impacts and other important effects. Coverage conditions such as practice guidelines or regulatory oversight can then reinforce the most promising models of care delivery.

Finally, an integrated policy approach is needed to address the significant societal consequences of genetic testing and related genomic technologies (41;47). Whether to cover a new genetic test is a piece of a much larger question about the role new genetic technologies should play in our culture, our economy, and our lives. Coverage decisions should be fashioned to fit with enduring values as well as other emerging genetic policies (e.g., privacy and patenting laws, laboratory and professional standards, resources for clinical infrastructure, etc.). An integrated policy approach would be equipped to address the collective interest as well as to adjudicate fairly and wisely between the competing concerns of the many stakeholders in genetic testing.

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