

Genome-wide Sequencing Ontario (GSO):

A protocol to compare genome sequencing technologies to improve rare disease diagnostics

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3 **Abstract** (250 words)
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5 **Background:** Genome-wide sequencing (GWS) has emerged as a promising strategy for
6 achieving timely diagnosis of rare diseases but is not yet available as a clinical test performed in
7 Canadian diagnostic laboratories. Motivated to establish high quality, timely, cost effective, and
8 equitable access to GWS for Ontarians, the *Genome-wide Sequencing Ontario (GSO)* pilot
9 project has developed an innovative, harmonized, multi-institutional model for delivering clinical
10 GWS. Herein we describe a protocol that aims to evaluate its performance in Ontario.
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19 **Methods:** A prospective cohort of patients will be enrolled over a two-year period. Eligible
20 cases for whom blood samples are available for the index case and both parents (i.e. trios) will be
21 randomized to receive exome (ES) or genome sequencing (GS). Patient and process-level data as
22 well as costs associated with the laboratory workflow for ES and GS will be ascertained. Point
23 estimates for diagnostic utility and timeliness will be compared statistically for ES and GS and
24 an incremental cost-effectiveness ratio, expressed as the incremental cost of GS compared to ES
25 per additional patient with a causal variant detected, will be determined.
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35 **Implications:** Findings from this work will provide robust evidence of diagnostic utility, cost
36 effectiveness, and timeliness of ES and GS. As the first Canadian study to compare the
37 performance of these clinical-grade technologies, findings will inform provincial and cross-
38 provincial policy related to the long-term organization, delivery, and reimbursement of genome-
39 based diagnostics for rare disease.
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Introduction

An accurate diagnosis is an essential component of care for rare disease patients, enabling tailored patient management, cascade family testing, family planning, and peer support (1).

Exome sequencing (ES) has emerged as a diagnostic test in many jurisdictions to facilitate diagnoses for patients with a suspected rare genetic disease (2-4). Extending the capabilities of ES, genome sequencing (GS) offers coverage of both coding and non-coding regions of the genome, and improved detection of copy number and structural variants (5). The term genome-wide sequencing (GWS) has emerged to refer to both ES and GS. In addition to its diagnostic capabilities, GWS can also identify secondary findings, defined as variants that are unrelated to the indication for testing but associated with medically actionable, often pre-symptomatic health risks (6). Despite the enhanced capabilities of GS compared to ES, a recent meta-analysis found that the diagnostic utility (i.e. rate of causative genotypes in known disease genes) of GS and ES were not significantly different (7). However, for both ES and GS, the likelihood of diagnosis was significantly greater when sequencing was performed on the index case plus two biological relatives (usually parents; referred to as trios) compared to the index case alone (i.e. referred to as singletons) (7). While studies of the cost effectiveness of ES and GS on a range of conditions are emerging (8-10), a recent systematic review of 36 studies concluded that the economic evidence base to support the use of ES and GS in the clinic is very limited and that robust comparative studies are urgently needed to support their translation into clinical practice (10).

Alongside this growing evidence base, the Ontario Ministry of Health (MOH), responsible for administering the health care system for Ontario's population of almost 15 million (11), has been instrumental in enabling access to clinical ES for Ontarians since 2014 through its Out-of-

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3 Country/Out-of-Province (OOC/OOP) Prior Approval Program (12). The OOC/OOP Prior
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5 Approval Program is an exceptional access mechanism that is in place in Ontario to allow the use
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7 of services outside the province or country when they are not available in the province and if
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9 specific criteria are met. These criteria are informed by relevant experts, stakeholders, and
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11 available professional best practice statements. In Ontario, criteria for access to ES were based
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13 on the Genetic Testing Advisory (GTAC) Committee's report (13), which itself was informed by
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15 the Canadian College of Medical Geneticists' (CCMG) Position Statement on the clinical
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17 implementation of GWS (14). In 2020, in response to the demand for local ES services, a
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19 comprehensive health technology assessment of ES and GS for unexplained developmental
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21 disabilities or multiple congenital anomalies was undertaken by Ontario Health. Based on the
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23 evidence reviewed in this assessment, the Ontario Health Technology Advisory Committee
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25 recommended public funding for ES as a second-tier test for these individuals (8,15).
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33 As a result of policy efforts and the evolution of exceptional access programs in Ontario and
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35 other Canadian provinces in recent years, approximately 1500 Canadian patients with rare
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37 disease, per year, receive access to clinical ES performed outside the country (16). While the
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39 approach to date has enabled access to high-quality ES in a significant subset of eligible patients,
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41 establishing local infrastructure is essential to enable the development of integrated laboratory
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43 services, a knowledge base that is locally representative, and a performance measurement system
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45 that will guide technical and policy decisions related to the use of this technology over time.
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48 Motivated to further optimize a high quality, timely, cost effective, equitable, and sustainable
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50 service for Ontarians, the objective of the *Genome-wide Sequencing Ontario* (GSO) protocol is
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52 to evaluate the clinical performance and cost effectiveness of ES and GS locally. The first of its
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3 kind in Canada, GSO will provide evidence to inform longer term technology adoption decisions
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5 in Ontario and serve as a model for evidence development and clinical translation in other
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7 jurisdictions for whom clinical GWS policy is a priority.
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10 11 12 **Methods**

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17 Informed by the strategies that have guided ES/GS implementation efforts internationally (17,
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19 18), we have developed a two-year, prospective, hybrid implementation-effectiveness study
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21 design tailored to Ontario's needs and resources (19). A design that blends components of
22
23 clinical effectiveness and implementation research, this approach enables more rapid
24
25 translational gains, more effective implementation strategies, and more useful information for
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27 decision makers (19). Although not designed as a hypothesis-driven effectiveness trial,
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29 participants are randomized to receive ES or GS to mitigate bias in determining and comparing
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31 performance and implementation outcomes for these sequencing strategies.
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38 39 Settings

40 GSO is co-hosted by the Genome Diagnostics Laboratories and Divisions of Clinical Genetics at
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42 The Hospital for Sick Children (SickKids) and The Children's Hospital of Eastern Ontario
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44 (CHEO) (Figure 1).
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49 50 Intervention: Genome-wide sequencing

51 Routine (i.e. non-rapid) ES and GS are performed on the Novaseq6000 sequencing platform at
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53 SickKids, followed by genome alignment and variant calling. Resulting variants undergo
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3 annotation, filtration, and interpretation. A cloud-based platform facilitates data flow between the
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5 laboratories, analysis and delivery, storage, and sharing. The harmonized interpretation and
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7 reporting protocols were developed by SickKids and CHEO laboratories based on technical
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9 specifications developed by an expert working group established by the MOH Laboratories and
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11 Genetics Branch (20).
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14 15 16 17 Participants 18

19 The target population includes adults and children and aligns with the eligibility criteria for GWS
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21 that are in use by Ontario's OOC/OOP Prior Approval Program, as established in the GTAC
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23 Report (13) and the CCMG Position Statement (14). Specifically, eligible patients include those
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25 for whom (a) a baseline genetics evaluation has been completed (e.g. phenotyping, family
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27 history, pretest genetic counselling and consent and, where indicated, chromosome microarray,
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29 targeted testing including biochemical testing), (b) a genetic etiology is the most likely
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31 explanation for the phenotype, as supported by a clinical presentation that includes any one of
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33 the following: (i) moderate to severe developmental or functional impairment, (ii) multisystem
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35 involvement, (iii) progressive clinical course which cannot be explained by another cause; or (iv)
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37 differential diagnosis that includes two or more conditions that would require evaluation by
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39 separate gene panels, and (c) blood samples from the index patient and both parents (i.e. trios)
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41 are available.
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49 Ineligible patients include those for whom (a) the clinical presentation is limited to: (i) isolated
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51 mild intellectual disability or learning disabilities, (ii) non-syndromic autism, (iii) isolated neuro-
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53 behavioural disabilities (e.g. attention deficit disorder), (iv) isolated neuropsychiatric conditions
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3 (e.g. schizophrenia) or (b) the phenotype is highly specific to a known genetic condition for
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5 which optimized genetic testing (e.g. multi-gene panel) exists or is suggestive of an aneuploidy,
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7 a methylation defect, or a trinucleotide repeat disorder. As an implementation project, the sample
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9 size (n=650) is based on the OOC/OOP Program annual testing volumes for SickKids and
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11 CHEO.
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17 Patients are enrolled prospectively and complete a clinical consent form that is harmonized
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19 across sites to enable data-sharing between SickKids and CHEO laboratories, optimizing the
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21 consistency of variant interpretation. Following completion of a genetics consultation during
22
23 which ES/GS is deemed indicated for a patient, the requisition and sample collection is
24
25 completed. All requisitions are reviewed by a genetic counsellor; if the patient meets eligibility
26
27 criteria, DNA is extracted and sent to the SickKids laboratory for sequencing. Requisitions for
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29 testing of cases with uncertain eligibility are reviewed by a joint committee of clinical and
30
31 laboratory experts. If eligibility criteria are not met, testing does not proceed, and a rejection
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33 report is issued to the ordering provider. For cases that are excluded, a physician can choose to
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35 appeal, whereupon the joint committee process would be used to evaluate any substantive
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37 additional clinical information or published evidence provided to support the case for testing. If
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39 preferred, ordering providers can submit a request for pre-approval prior to sample collection.
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46 47 Randomization and matching 48

49 Patients are randomly assigned to ES or GS using a 1:1 ratio and an un-blinded stratified
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51 permuted block randomization design. Cases are stratified by clinical site, phenotype, and
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3 molecular testing history. Depending on the expected recruitment in each stratum, block sizes
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5 (i.e. number of patients in each strata) are 2, 4 or 6.
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10 Data Collection

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12 A centralized REDCap database has been developed to capture a wide range of patient-level
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14 process and outcome measures to enable the assessment of three core dimensions on quality care:
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16 diagnostic utility, timeliness, and cost-effectiveness (21). Patient-level data include: (i) clinical
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18 characteristics (i.e. enrolment site, age, physical features/symptoms, ethnicity, consanguinity,
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20 molecular testing history, test urgency), (ii) patient preferences related to research re-contact and
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22 receipt of secondary findings, (iii) number and characteristics of primary variants identified, and
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24 (iv) number and characteristics of secondary findings identified. Patient characteristics and
25
26 preferences related to research recontact and receipt of secondary findings will be ascertained
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28 from ES/GS requisition forms that are submitted to the laboratory and the result of the ES/GS
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30 analyses will be obtained from the harmonized, cloud-based genome analysis platform.
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38 Process measures include details related to: (i) sample accessioning (i.e. date samples
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40 received/accessioned,) (ii) genome analysis (i.e. dates analysis initiated and completed, date
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42 results reported, time required for analysis), and (iii) segregation analysis (i.e. dates initiated and
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44 reported, number of samples included, variant classification, parental inheritance). Process
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46 measures will be ascertained from the SickKids and CHEO laboratory information systems. Data
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48 collection will be facilitated by members of the study team and monitored monthly for data
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50 accuracy and completion. Missing data identified through quality checks will be obtained by the
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3 laboratory genetic counsellor from the ordering provider, technologist, genome analyst, or
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5 director assigned to the case.
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10 Costs for ES and GS will be determined by microcosting of laboratory workflow components for
11 each sequencing approach (8, 15, 22, 23). Data on the volume of resource use and unit price for
12 each workflow input will be obtained from laboratory protocols and managers. Diagnostic utility
13 will be defined as the rate of causative, pathogenic, or likely pathogenic genotypes in known
14 disease genes and reported as the proportion of cases for whom diagnostic, partially diagnostic,
15 and medically-actionable secondary variants are identified. Timeliness will be defined from a
16 laboratory perspective and measured as the number of weeks elapsed from sample accessioning
17 to laboratory reporting and will be reported as the proportion of cases for whom laboratory
18 turnaround time is <12 weeks. Cost-effectiveness will be reported as the incremental costs of
19 local GS compared to ES per additional patient with a molecular diagnosis achieved.
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35 Statistical Analysis

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37 We will analyse our data using descriptive statistics (mean, median, range and standard
38 deviation). Point estimates for diagnostic utility and timeliness will be compared statistically for
39 ES and GS. We will examine the relationship between clinical characteristics (e.g. age, age of
40 onset, sex, phenotype, prior testing history) and diagnostic yield using parametric or non-
41 parametric univariate statistics as appropriate. If indicated, we will explore explanatory variables
42 of diagnostic utility using a regression model. A cost per trio ES and cost per trio GS will be
43 determined. Costs for each input related to the ES and GS laboratory workflows will be
44 calculated by multiplying resource volume by unit price. For labour, time in minutes for each
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3 task will be multiplied by wage rates. The most recently available price units will be used (2021).
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5 Otherwise, the prices as reported in previous microcosting studies (22, 23) will be assumed to be
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7 stable based on consultation with lab managers. The costs of laboratory workflow inputs for each
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9 sequencing approach will be summed to determine a per sample cost. A cost-effectiveness
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11 analysis will be undertaken from an institutional payer perspective in which the difference in
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13 costs between GS and ES will be calculated and divided by the difference in diagnostic yield to
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15 calculate an incremental cost-effectiveness ratio expressed as the incremental cost of GS
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17 compared to ES per additional patient with a pathogenic variant detected. As an implementation
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19 project, this CEA is limited to laboratory costs and outcomes. Given the complexity of diagnostic
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21 outcomes and the heterogeneity of the patient sample, it will not be possible to model patients'
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23 health states and the range of treatment options that might ensue from a given diagnostic result to
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25 generate health benefits, such as QALYs, over a lifetime. All costs will be reported in 2021
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27 Canadian dollars (CAD). SQUIRE reporting guidelines will be used (24).
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35 Ethics Approval

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37 Individuals undergoing GWS as part of this protocol provide clinical consent for GWS and
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39 research consent through Clinical Trials Ontario [CTO-1577]; CTO is the provincial body
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41 responsible for approving clinical trials and observational studies involving two or more
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43 academic or health care institutions in Ontario.
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49 **Interpretation**

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51 This is the first Canadian study to compare the performance of these technologies and will be
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53 instrumental in guiding provincial policy and funding decisions related to their ongoing use in
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3 clinical care. Findings from this work will provide robust evidence of diagnostic utility, cost
4 effectiveness, and timeliness of clinical grade ES and GS. The relationship between key clinical
5 characteristics (e.g. age, age of symptom onset, phenotype, prior testing history) and these
6 performance outcomes will also be assessed to understand the relative performance of these
7 technologies in different patient groups. In particular, our data will inform the development of
8 diagnostic pathway guidelines for the use of ES and GS for different clinical indications and
9 when the pathway should include ES versus GS. Finally, having established a centralized
10 sequencing-distributed interpretation model between two sites, data collected herein will inform
11 the feasibility and costs of scaling this model across the province.
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26 **Knowledge Translation**

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28 In addition to disseminating our findings through academic publications and presentations, we
29 will generate a report for the provincial policy partners who have been engaged in the design and
30 implementation of this work. We will also develop educational materials for an expanding
31 network of ordering providers to improve genomic literacy among non-genetics providers and
32 generate lay summaries of our findings for the rare disease patient community.
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42 **Limitations**

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44 The primary limitations of this work relate to the inclusion of cases from only two clinical sites
45 in Ontario and the restricted inclusion criteria. With an emphasis on pediatric patients with
46 neurodevelopmental phenotypes, findings related to the performance of ES and GS may be
47 limited in their generalizability to adult patients with rare disease and to those with non-
48 neurodevelopmental phenotypes.
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Opportunities for future research

All patients are provided with the option to participate in future research as part of their clinical consent process. Patients that consent to re-contact are able to enrol in additional REB-approved studies linked to GSO including: (a) clinical re-analysis of genomic data and (b) the patient and system impacts of medically actionable secondary findings. Findings from these particular studies will inform best practices and guidelines for clinical re-analysis and for managing secondary findings in a single-payer healthcare system. GSO participants will also be able to enrol in other rare disease research initiatives focused on gene discovery, characterizing natural history, and trialing precision therapies (25).

Conclusion

This protocol lays the foundation for ongoing development and implementation of clinical ES and GS technologies. Moving beyond Ontario, we will engage our clinical, research, policy, and funding partners to understand province-specific barriers and facilitators of ES and GS implementation and strategize – as a community of practice invested in the equitable and sustainable delivery of high-quality genomic medicine – to develop concrete implementation structures and processes for Canadians. Going forward, our evaluation framework will not only serve to monitor performance and inform continuous system improvement, it will also guide our evaluation of emerging -omic technologies and applications in the years to come.

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3 **Data-Sharing Statement:** As data collection is underway, data are not currently available to or
4 accessible by others.
5

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7 Ho and Ms. Neeta Sarta as representatives of the Laboratory and Genetics Branch, Ontario
8
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15 **Contributor's Statement:**

16 RZH, CRM, MKG, AS, CC, JS, EMP, RK, WL, LH, OJ, WJU, RM, MS, KMB contributed
17 substantially to conception and design
18

19 RZH, CRM, MKG, AS, CC, JS, EMP, RK, WL, LH, OJ, WJU, RM, MS, KMB drafted the
20 article or revised it critically for important intellectual content
21

22 RZH, CRM, KMB, MS gave final approval of the version to be published
23

24 RZH, CRM, KMB, MS agreed to act as guarantor of the work (ensuring that questions related to
25 any part of the work are appropriately investigated and resolved).
26
27

28
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36 **LIST OF FIGURES**
37

38 Figure 1: GSO Structure and Settings (see attached ppt file)
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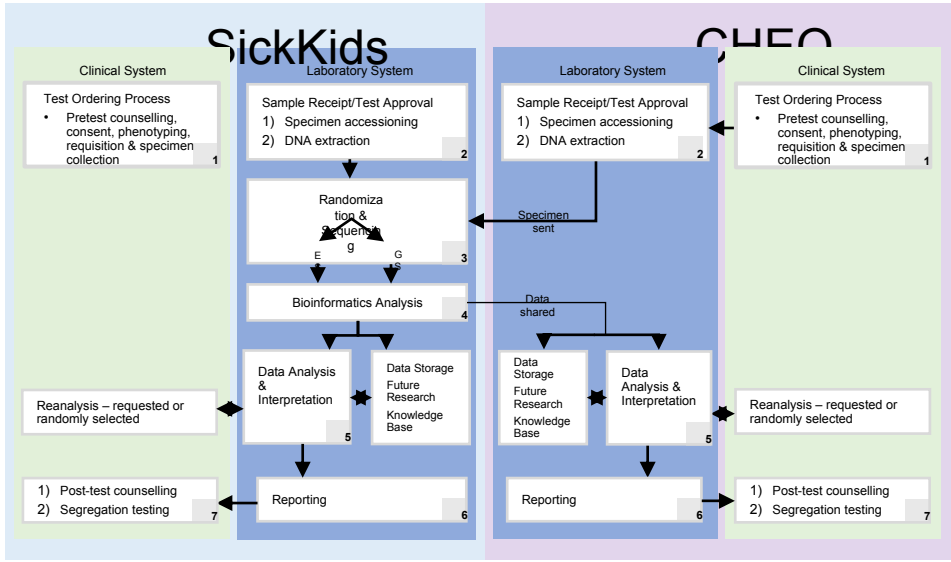


Figure 1: GSO's harmonized, multi-institutional model for delivering GWS
 GS = genome sequencing, ES = exome sequencing

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