Proposed Protocol: Network-wide implementation of GARDE for population-based genetic testing.

GARDE has successfully enabled population-based genetic testing for 2 of the CDC's 3 Tier 1 genomic medicine applications at the UU and New York University: hereditary breast/ovarian cancer testing and Lynch syndrome testing.[1,2] GARDE is being implemented at multiple additional sites, including a safety-net care setting, to support this priority genomic medicine use case (U24 CA274582). While GARDE could be used to support any population-based genetic testing priority identified by the gLHS Network, we propose leveraging GARDE for the remaining CDC Tier 1 genomic medicine application not yet addressed by GARDE: FH testing.

Clinical Importance of FH and Genetic Testing for FH. FH is the most common autosomal dominant genetic disease, affecting approximately 1 in 300 individuals.[3] FH is caused by a functional mutation in one or more genes that break down low-density lipoprotein cholesterol (**LDL-C**). FH markedly increases the risk of coronary artery disease (**CAD**), the most common cause of death among US adults.[4] If not identified and treated, men have a ~50% risk of a fatal or nonfatal CAD event by age 50 and women have a ~30% risk by age 60.[5,6] Even when controlled for LDL-C levels, patients with FH have a markedly higher risk of CAD; individuals with LDL-C $\geq$ 190 mg/dL and a FH mutation have 22-fold increased risk of CAD compared to those with LDL-C < 130 mg/dL and no mutation, vs. a 6-fold increased risk for those with LDL-C $\geq$ 190 mg/dL and no FH mutation.[7]

Identifying patients with a FH mutation has multiple benefits: it provides key prognostic information; it leads to greater pharmacotherapy initiation, therapy adherence, and LDL-C reduction; it enables family-based cascade testing; and it provides an indication for more intensive lipid-lowering therapy, including through use of PCSK9 inhibitors.[8] Despite the benefits of diagnosis, > 90% of the > 1 million Americans with FH are undiagnosed.[9,10]

American College of Cardiology (ACC) Guideline on FH Testing. We propose population-based genetic testing for FH adapted from the 2018 ACC guideline.[8] The ACC guideline calls for offering genetic testing for FH for adults when they (1) have LDL-C levels $\geq$ 190 mg/dL with at least 1 first-degree relative with premature CAD or (2) have LDL-C levels $\geq$ 250 mg/dL in the absence of a positive family history.[8]

GARDE Architecture and Information Flow. The standards-based GARDE architecture and information flow have been previously described,[1,11] and is summarized in **Figure 2**. In step 1, the GARDE Population Coordinator runs an EHR database query to identify the screening population (e.g., patients seen in the past year with an LDL-C result available and a patient portal account). In step 2, relevant patient data are retrieved from the EHR and converted to the HL7 FHIR format (the FHIR data could potentially be directly extracted using the Bulk FHIR standard[12] as it matures). In step 3, an OpenCDS-based CDS Hooks service is used to evaluate the patients in bulk to identify if they meet guideline criteria for FH genetic testing. Natural language processing (**NLP**) can also be used to process free text data such as provider comments on the age of onset of CAD in a family member.[40] In step 4, these conclusions are exported into the EHR's population health registry. In step 5, this registry is used to manage the population. Patient portal messages are sent and a chatbot is used to offer and facilitate genetic testing.

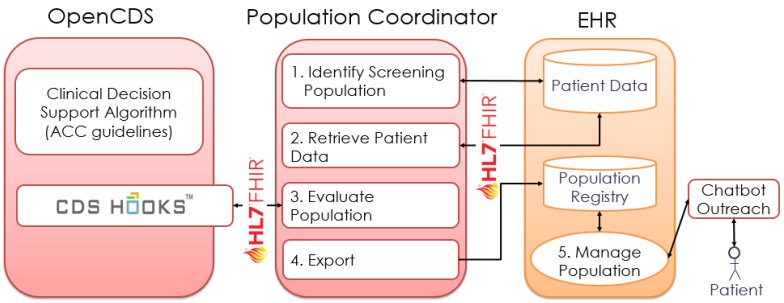

Figure 2. GARDE Architecture

Chatbot-Facilitated Genetic Testing Process. Once patients in need of genetic testing are identified, patient portal messages are sent in batch inviting them to learn about testing through an automated assistant (**Figure 3**). Patients interact with a chatbot to learn more about testing, and if they are interested, they are provided with information on how to get tested through an at-home mail-in saliva testing kit. After testing, patients with negative results are provided with chatbot-based post-testing education, while patients with positive or

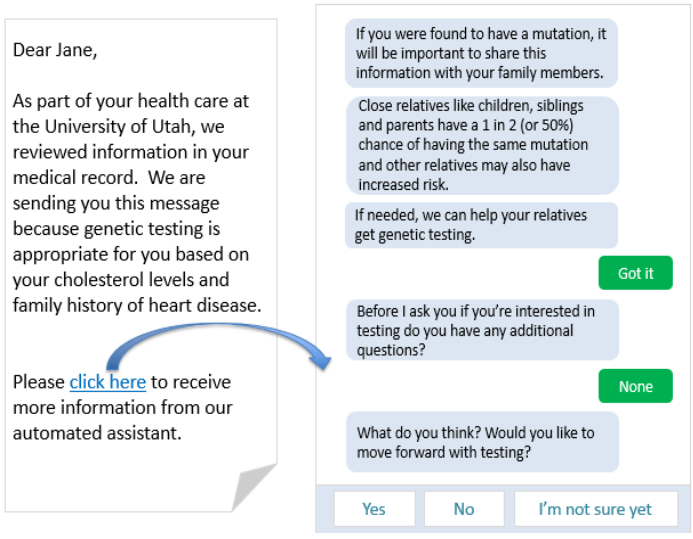

Figure 3. Sample outreach message and chatbot interaction

uncertain results are contacted by the genetic counseling team for follow-up. Patients can request to speak to the genetic counseling team at any point. The effectiveness of this approach has been demonstrated at two institutions as a part of the BRIDGE trial.

Implementation and Evaluation. There are 4,521 adult patients who were seen at a UU primary care clinic in the past year, have an active patient portal account, and have an LDL-C of ≥ 190 mg/dL on record. Of these patients, 610 meet the strictest interpretation of the ACC testing criteria (e.g., LDL-C ≥ 190 mg/dL and documentation of first degree relative with heart disease age of onset ≤ 55 for men and ≤ 65 for women). Further, 1,958 meet the criteria if age of onset is assumed to be ≤ 55 for men and ≤ 65 for women. We propose targeting the broad population of patients with an LDL-C ≥ 190 mg/dL for genetic screening, as 1) relatives with FH may increasingly experience heart disease at a later age due to improving LDL-C control over time,[13,14] 2) we have found there are sex, racial, ethnic, and language disparities in the completeness of family health history recorded in the EHR,[15] and 3) these patients are currently offered FH genetic testing by the UU cardiovascular genetic counseling service when referred for evaluation. As was done in BRIDGE, we propose full support for both English and Spanish.

For the 4,521 patients with an LDL-C ≥ 190 mg/dL on record, only 15 (0.3%) have undergone FH genetic testing. We propose randomizing the remaining 4,506 patients to usual care or GARDE outreach, with a waiver of informed consent as we are evaluating the impact of increasing the uptake of an evidence-based intervention (i.e., FH genetic testing) that is standard of care. In order to support iterative learning and re-implementation, we propose a two-phase study, with phase 1 including one half of the eligible population (i.e., 2,253 patients) and phase 2 including the other half. Eligible patients will be randomly assigned to the two phases, and within each phase, patients will be randomized in a 1:1 ratio to usual care vs. GARDE outreach. Between phases 1 and 2, the lessons learned from phase 1 (e.g., via patient interviews) will be incorporated into an enhanced intervention for phase 2 re-implementation.

The primary outcome will be genetic testing for FH. Secondary outcomes will include chatbot adoption/use and identification of a pathogenic FH mutation.[7] Based on our experience in the BRIDGE trial, we anticipate 26% of patients randomized to GARDE outreach will complete the chatbot-facilitated pre-test education and 13% will undergo genetic testing in Phase 1. We aim for 23% undergoing genetic testing in Phase 2. Patients identified with a pathogenic FH mutation will serve as the nucleus for standard-of-care cascade testing of relatives. We will provide estimates of the proportions undergoing FH genetic testing by treatment arm in each phase, with 95% binomial confidence intervals. Given the very large hypothesized effect sizes (13% vs. 0.3% in phase 1, and 23% vs. 0.3% in phase 2), statistical power is essentially 100% to confirm between group differences within each phase, so we will primarily emphasize the estimated rates of genetic testing with their associated confidence intervals under the GARDE outreach intervention. The study also has > 99% power (with 2-sided $\alpha = 0.05$) to detect the hypothesized 10% increase in the proportion with FH genetic testing between the GARDE outreach treatment arms for phase 2 compared to phase 1.

Use Case Flexibility. Given the versatility of GARDE, we will be able to support any population-based genetic testing priority selected by the Network, whether it be FH, hereditary cancer, or another high priority condition.

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