The Genetic Testing Reference Materials Coordination Program (GeT-RM)-A sustainable community process to improve availability of appropriate reference materials for genetic testing

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BACKGROUND

The expansion of molecular genetic testing in clinical and public health practice has increased the need for appropriate, characterized cell line/genomic DNA materials for quality assurance, test validation, proficiency testing, and development of new genetic tests. However, despite the growing test volume and the rapidly increasing number of tests being offered, the necessary reference materials are not available for the vast majority of tests.

METHOD/RESULTS

The Genetic Testing Reference Materials Coordination Program (GeT-RM)

The U.S. Centers for Disease Control and Prevention (CDC), in collaboration with members of the genetic testing community, has developed a program to improve public availability of reference materials and to facilitate information exchange and communication on reference material development, contribution, characterization, distribution, and needs assessment. This CDC-based Genetic Testing Reference Material Coordination Program (GeT-RM) provides continuing support and coordination to improve reference material availability.

The GeT-RM Program:

1) Facilitates the identification, procurement, development, characterization and distribution of needed reference materials;

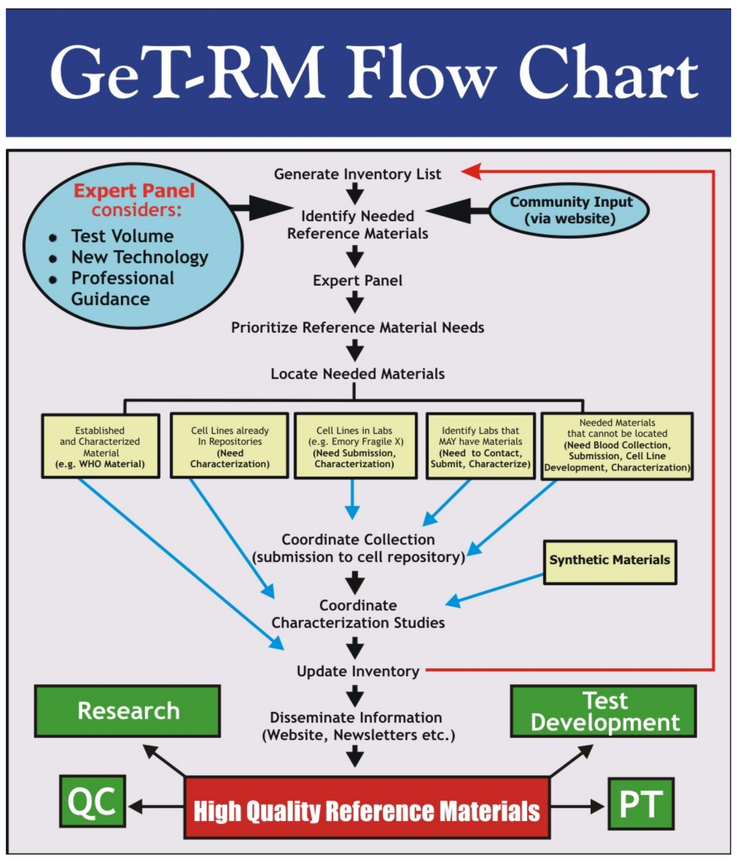
2) Facilitates exchange of reference material related information;

3) Explores collaborative efforts for ongoing needs monitoring and materials development.

The GeT-RM Reference Material Development Process (Figure 1)

1. Reference material needs are identified
2. Needed materials are located or obtained
3. Cell culture and DNA preparation is performed by the Coriell Cell Repositories (Coriell)
4. DNA is sent to volunteer clinical testing laboratories for characterization of mutations or target sequences
5. Reference materials and information are made available to genetic testing community

Figure 1.



GeT-RM Program Components

The Expert Panel
An expert panel, consisting of representatives from professional organizations, PT EQA programs, government, research, cell banks, industry and genetic testing laboratories provides advice to the GeT-RM program. This group also helps to prioritize the reference material needs.

GeT-RM Website:
http://www.cdc.gov/dls/genetics/rmmaterials/default.aspx

This interactive website facilitates collection of information about community reference material needs, disseminates information about the availability of reference materials, provides links to professional, practice and regulatory guidelines for genetic testing and solicits involvement of the genetics community in the project.

Current (or recently completed) GeT-RM Reference Material Development Projects:

Huntington Disease (HD)
The CAG repeat lengths in 14 HD cell lines were measured by assays in 10 clinical genetic testing laboratories and by DNA sequence analysis. The repeat lengths in these cell lines represent a large range of sizes that include important diagnostic cutoffs and allele combinations. Cell lines/DNA characterized by this project are available from Coriell's NIGMS Human Genetic Cell Repository.

Ashkenazi Jewish Disorders
Thirty-one cell lines were selected from Coriell that represent many of the commonly tested alleles for Tay-Sachs disease, Canavan disease, familial dysautonomia, Mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia type C, Bloom syndrome, Gaucher disease, and glycogen storage disease. Three to 6 laboratories (depending on the composition of their test panels) independently tested DNA from the 31 cell lines. Two laboratories used home-brew PCR based assays and four of the 6 laboratories incorporated a commercially available ASR into their assay (Tag-It, Tm Bioscience). Twenty-five different disease alleles were identified. Cell lines/DNA characterized by this project are available from Coriell's NIGMS Human Genetic Cell Repository.

Fragile X (FX)
Fifteen FX cell lines, representing a variety of repeat lengths in the normal and premutation range, were donated to Coriell's NIGMS Human Genetic Cell Repository by Dr. Stephanie Sherman, Emory University. Each of 9 clinical laboratories determined the CGG repeat length(s) of the 15 FX cell lines and 6 Coriell FX lines using their in-house assay and an ASR developed by Celera Diagnostics. DNA sequence analysis was also performed. These materials are available from Coriell's NIGMS Human Genetic Cell Repository.

Cystic Fibrosis (CF)
Coriell has cell lines that have been characterized by DNA sequence analysis for the 23 alleles recommended by ACMG/ACOG. To complement this, we selected alleles commonly included in commercial CF panels that are not included in the 23 ACMG/ACOG alleles. Seven cell lines were selected from those existing at Coriell and 6 were created specifically for this project. The CF alleles in these materials were confirmed by testing in 7 volunteer laboratories using a variety of assay platforms, including DNA sequence analysis. Thirteen alleles not included in the ACMG 23 panel were identified in the DNA samples. These materials are available from Coriell's NIGMS Human Genetic Cell Repository.

GeT-RM
Genetic Testing Reference Materials
PROGRAM

Disorders on the ACMG Newborn Screening Panel
10 Coriell cell lines containing common point mutations in genes causing Congenital Adrenal Hyperplasia (CAH), Galactosemia, Medium Chain Acyl-CoA Dehydrogenase (MCAD), and Maple syrup urine disease (MSUD) have been characterized in 4 or 5 clinical laboratories using a variety of methods including DNA sequence analysis. An additional 16 samples representing 11 disorders will be characterized by DNA sequence analysis in the near future.

Pharmacogenetic polymorphisms
Data on the pharmacogenetic genotype of publicly available cell lines and commercially available products was collected from the genetic testing community. Tables listing hundreds of cell lines typed for different combinations of pgx loci (CYP2D6, CYP2C9, CYP2C19. VKORC1, UGT1A1) are presented on the GeT-RM website.

Future GeT-RM Reference Material Development Projects

Cell lines and DNA for the following disorders are currently being collected and prepared for reference material development:

MEN2

BRCA1

BRCA2

Y deletions

MTHFR

Factor VHR2

Alpha1 antitrypsin

Long Chain L3 hydroxy Acyl-CoA Dehydrogenase (LCAD)

Other Available Reference Materials

- Many cell lines containing characterized or uncharacterized mutations are available from cell repositories. The GeT-RM website provides information on these resources.
- The CDC, through a contract to Duke University, developed 27 characterized cell lines for QC use. These cell lines are associated with cystic fibrosis, Connexin 26, Craniosynostosis/Muenke Syndrome, Hemochromatosis, Huntington Disease, MTHFR and alpha-thalassemia. These are available from Coriell (CDC respository).

CONCLUSIONS

- Reference materials are needed to improve the quality and availability of clinical genetic testing
- Reference materials are needed for development and assessment of new genetic tests
- The GeT-RM will work to meet these needs by facilitating development of characterized reference materials, fostering communication between users of reference materials, and raising awareness of reference material availability

More Info- GeT-RM Website:
http://www.cdc.gov/dls/genetics/rmmaterials/default.aspx