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Development of Genomic DNA Reference Materials for Genetic Testing of Disorders Common in People of Ashkenazi Jewish Descent

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Many recessive genetic disorders are found at a higher incidence in people of Ashkenazi Jewish (AJ) descent than in the general population. The American College of Medical Genetics and the American College of Obstetricians and Gynecologists have recommended that individuals of AJ descent undergo carrier screening for Tay Sachs disease, Canavan disease, familial dysautonomia, mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia type C, Bloom syndrome, and Gaucher disease. Although these recommendations have led to increased test volumes and number of laboratories offering AJ screening, well-characterized genomic reference materials are not publicly available. The Centers for Disease Control and Prevention-based Genetic Testing Reference Materials Coordination Program, in collaboration with members of the genetic testing community and Coriell Cell Repositories, have developed a panel of characterized genomic reference materials for AJ genetic testing. DNA from 31 cell lines, representing many of the common 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, was prepared by the Repository and tested in six clinical laboratories using three different PCR-based assay platforms. A total of 33 disease alleles was assayed and 25 different alleles were identified. These characterized materials are publicly available from Coriell and may be used for quality control, proficiency testing, test development, and research. ***(J Mol Diagn 2009, 11:530–536; DOI: 10.2353/jmoldx.2009.090050)***

Many ethnic groups have genetic disorders that are overrepresented due to founder effects. Examples include cystic fibrosis and α-1-antitrypsin deficiency in European Caucasians,[1,2] and α or β thalassemia in groups living in equatorial regions with endemic malaria (Medical Genetics Information Resource, *http://www.genetests.org,* last accessed May 4, 2009).[3]

Ashkenazi Jewish (AJ) individuals are the descendents of those belonging to the Hebrew ethnic and religious group that settled in Eastern Europe in the early Middle Ages. Several autosomal recessive disorders are more common in the AJ population than in the general population (Table 1).[4–6] An estimated one in 4.8 AJ individuals is a carrier of one of these diseases,[8] most of which are severe and cause significant morbidity and mortality. Treatment to reduce symptoms and prolong life is available for some of these disorders, and novel treatments and therapies, including enzyme replacement therapy, have recently become available or are in development.

Most cases of these diseases in the AJ population are due to one or a few disease causing alleles. For example, three mutations account for approximately 95% of Niemann Pick (NP) chromosomes in the AJ population, while there is no common mutation associated with NP in the general population (Table 1). Similarly, five mutations in the *CFTR* gene account for approximately 97% of cystic fibrosis alleles in the AJ population, whereas a set of 25 mutations accounts for only 90% in

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Table 1. Alleles Included in Clinical Ashkenazi Jewish Testing Panels

Disorder	Gene	Alleles on clinical AJ panels	Allele frequency in affected AJ population	AJ heterozygote frequency (all alleles)	Allele frequency in affected non-AJ population	Allele found in DNA samples studied
BS	*BLM*	2281del6/ins7 NM_000057.2:c.2340delATCTGA.insTAGATTC	>99%[7]	1:107,[7] 111,[13] 157[8]		Yes
CD	*ASPA*	E285A NM_000049.2:c.854A>C	82.9%[9]	1:37,[8] 38,[11] 65[10]	2.5%[9]	Yes
CD	*ASPA*	Y231X NM_000049.2:c.693C>A	14.8%[9]		0.0%[9]	Yes
CD	*ASPA*	A305E NM_000049.2:c.914C>A	0%[9]		60%[9]	Yes
CD	*ASPA*	433(−2)A>G (IVS2-2) NM_000049.2:c.433–2A>G	1.1%[9]		0.0%[9]	No
FA	*FACC*	IVS4(+4)A>T NG_011707.1:g.82053A>T	>99%[12]	1:77,[8] 89,[12] 92[13]		Yes
FA	*FACC*	322delG NM_000136:c.67delG				Yes
FD	*IKBKAP*	IVS20+6T>C (2507+6T>C) NG_008788.1:g.40664T>C	98%[8]	1:29,[8] 31[6]		Yes
FD	*IKBKAP*	R696P NP_03631.2:p.R696P	2%[8]			No
GD	*GBA*	N370S NM_000157.2:c.1226A>C	85%[5]	1:17,[8] 18[10]		Yes
GD	*GBA*	84GG (1035insG) NM_000157.2:c,93_94insG	6%[5]			Yes
GD	*GBA*	L444P NM_000157.2:c.1448T>C	3.5%[5]			Yes
GD	*GBA*	IVS2+1G>A NM_000157.2:c.27+1G>A	1%[5]			Yes
GD	*GBA*	R496H NM_000157.2:c.1604G>A				No
GD	*GBA*	D409H NM_000157.2:c.1343A>T				No
GD	*GBA*	V394L NM_000157.2:c.1297G>T				Yes
GD	*GBA*	del55bp NM_000157.2:c.1263del55				No
MLIV	*MCOLN1*	IVS3-2A>G NM_020533.1:c.406-2A>G	66%[14]	1:67,[8] 100,[15] 127[14]		Yes
MLIV	*MCOLN1*	del6434(ex1-7) AF_287270:g.511-6943del	30%[14]			Yes
NP	*SMPD1*	R496L NP_000534.3:R496L	97%[16,10]	1:90,[16] 103,[8] 125[10]		Yes
NP	*SMPD1*	fsP330 NM_00543.2:c.990delC				Yes
NP	*SMPD1*	L302P NP_000534.3:L302P				Yes
NP	*SMPD1*	delR608 NP_000534.3:R608del				Yes
TSD	*HEXA*	1278+TATC M_16411:c.1278.insTATC	81%[17]	1:31[17]	32%[17]	Yes
TSD	*HEXA*	IVS12+1G>C M_16421:g.200G>C	15%[17]			Yes
TSD	*HEXA*	G269S M_16411:c.805G>A	2%[17]			Yes
TSD	*HEXA*	IVS9(+1)G>A M_16417:g.149G>A	0%[17]		14%[17]	Yes
TSD	*HEXA*	R247W (pseudo) M_16411:c.739C>T	0%[17]			Yes
TSD	*HEXA*	R249W (pseudo) M_16411:c.745C>T	0%[17]			No
TSD	*HEXA*	del7.6kb NT_010194:g.del70457939-70449986				No
TSD	*HEXA*	IVS7+1G>A M_16417:g.149G>A				No
GSD	*G6PC*	R83C NM_000151.2:c.247C>T	~100%[18]	1:71[18]		Yes
GSD	*G6PC*	Q347X NM_000151.2:c:1039C>T				Yes

AJ, Ashkenazi Jewish; BS, Bloom Syndrome; CD, Canavan Disease; FA, Fanconi Anemia; FD, familial dysautonomia; GD, Gaucher disease; MLIV, mucolipidosis type IV; NP, NP disease type A; TSD, Tay-Sachs disease; GSD, glycogen storage disorder type Ia.

the Northern European population (and significantly less in other populations).[19,20] Molecular testing for many of the disorders common in the AJ population has been developed and is currently in widespread use.

The American and Israeli Jewish communities have been highly supportive of population-based carrier testing and reproductive genetic counseling for carriers. Tay-Sachs disease (TSD) is the first genetic condition for which community-based carrier detection was implemented.[17,21] In Jewish communities around the world, couples are urged to participate in screening before pregnancy and, in some cases, before marriage. Now 30 years old, carrier screening for TSD is the longest-running, population-based program designed to prevent a lethal genetic disease. Screening has reduced the number of TSD cases in the United States and Canada by 90% (Genome News Network, *http://www.genomenewsnetwork.org/articles/08_01/Tay_Sachs_gene_tests.shtml,* last accessed March 9, 2009).

In 2004, the American College of Obstetricians and Gynecologists recommended that individuals of AJ descent undergo prenatal and preconceptional carrier testing for TSD, Canavan disease (CD), familial dysautonomia (FD), and cystic fibrosis. Testing for mucolipidosis type IV (MLIV), NP disease type A, Fanconi anemia (FA) group C, Bloom syndrome (BS), and Gaucher disease (GD) was also suggested.[22] Although glycogen storage disorder type 1a (GSD) testing has not been recommended by American College of Obstetricians and Gynecologists, many laboratories offer this analysis because testing for two alleles, R83C and Q347C, in the *G6PC* gene can detect almost 100% of affected patients in the AJ population. In addition to the American College of Obstetricians and Gynecologists recommendations, the American College of Medical Genetics has recommended carrier testing for cystic fibrosis, CD, FD, TSD, and suggests that screening should be offered for FA, NP, BS, MLIV and GD.[23] Many molecular genetics laboratories currently offer testing for some or all of these disorders and often multiplex them into a single testing panel. More laboratories are expected to offer testing as the demand increases.

A variety of assay methods, including commercial analyte specific reagents and laboratory developed tests (LDTs) are in use. As with other genetic diseases, laboratories testing for AJ disorders often find it difficult to obtain reference materials (RMs) or quality control (QC) materials for test development, validation, QC, and proficiency testing/external quality assessment. This is due to the relative rarity of affected patients, paucity of archived samples in research laboratories, and lack of materials available from repositories.

To address the lack of RMs for AJ panel testing, the Centers for Disease Control and Prevention-based Genetic Testing Reference Materials Coordination Program (GeT-RM), in collaboration with members of the genetic testing community and the Coriell Cell Repositories, have created a set of 31 genomic DNA materials with confirmed mutations. These RMs were selected to include alleles representing nine disorders (BS, CD, FA, FD, GD, MLIV, NP, TSD and GSD) commonly included in clinical AJ testing panels. The alleles in these samples were confirmed by six volunteer laboratories using a variety of methods. A separate set of materials with characterized cystic fibrosis mutations has been developed and is reported separately.[24]

Materials and Methods

Cell Lines and DNA Preparation

The RM needs for AJ genetic testing were defined by consultation with clinical laboratory directors, analysis of current test panels, and assessment of available QC and RMs. Based on this analysis, 20 Epstein-Barr virus transformed lymphoblast cell lines and 11 fibroblast cell cultures were selected from the National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository at the Coriell Cell Repositories (*http://ccr.coriell.org/Sections/Collections/NIGMS/?Ssid=8*, last accessed April 10, 2009). These cell lines carry many of the commonly tested alleles causing the nine disorders included in this study (Table 2).

The cell lines were cultured using previously described methods.[25] Approximately 1 to 2 mg of DNA was prepared from each of the selected cell lines by the Coriell Cell Repositories.[26]

Laboratory Selection

Six commercial or academic clinical genetic laboratories offering AJ Panel testing volunteered to participate in this mutation confirmation study. All six of the laboratories were in the United States and were accredited by the College of American Pathologists.

Protocol

Each of the testing laboratories received blinded, 50 μg aliquots of DNA from each of 27 AJ cell lines. The laboratories assayed the DNA samples one time using their current in-house method. The results were sent to the study coordinator (L.K.), who compiled the data and checked for discrepancies.

After the initial set of 27 DNA samples was tested, an additional four DNA samples (GM00059, GM01031, GM09787, and GM04863) containing mutations not identified in the initial materials became available from Coriell. Aliquots of these samples (Batch 2) were sent to four of the participating laboratories for testing. The assays used in these four laboratories represent all of the methods used with the initial 27 samples.

Assay Methods

DNA from each of the 31 cell lines was tested by three to six of the participating laboratories (depending on the disorders included in their AJ test panels). The disorders/alleles included in each assay are shown in Table 3. Four of the six laboratories used an assay based on commercially available reagents (xTAG) from Luminex Molecular

Table 2. Results of AJ Reference Material Characterization Study

Disorder	Gene	Coriell cell line #	Allele 1 (# labs)*	Allele 2 (# labs)*	Other mutations† (# labs)*
BS	*BLM*	GM03403	2281Del6/Ins7 (6)	2281Del6/Ins7 (6)	
BS	*BLM*	GM04408	2281Del6/Ins7 (6)	—	
CD	*ASPA*	GM04268	E285A (6)	E285A (6)	
CD	*ASPA*	GM17821	E285A (6)	—	
CD	*ASPA*	GM18929	Y231X (6)	—	
CD	*ASPA*	GM00059	A305E (4)	—	
FA	*FACC*	GM00449	IVS4(+4)A>T (6)	IVS4(+4)A>T (6)	
FA	*FACC*	GM12794	322DelG (4)	—	
FD	*IKBKAP*	GM05046	IVS20(+6)T>C (6)	—	
FD	*IKBKAP*	GM05106	IVS20(+6)T>C (6)	IVS20(+6)T>C (6)	
GD	*GBA*	GM00852	84G>GG (6)	N370S (6)	
GD	*GBA*	GM01607	N370S (6)	V394L (4)	
GD	*GBA*	GM04394	L444P (6)‡	—	
GD	*GBA*	GM08752	L444P (6)	L444P (6)	
GD	*GBA*	GM10870	N370S (6)	N370S (6)	
GD	*GBA*	GM01031	IVS2+1G>A (4)	—	
GSD	*G6PC*	GM11215	Q347X (3)	Q347X (3)	
GSD	*G6PC*	GM11468	R83C (3)	Q347X (3)	
GSD	*G6PC*	GM11470	R83C (3)	—	
GSD	*G6PC*	GM11471	Q347X (3)	—	
MLIV	*MCOLN1*	GM02528	IVS3(−2)A>G (6)	IVS3(−2)A>G (6)	Gaucher N370S (5)
MLIV	*MCOLN1*	GM02533	IVS3(−2)A>G (6)	Del6.4Kb (6)	
NP	*SMPD1*	GM00112	L302P (6)	L302P (6)	
NP	*SMPD1*	GM03252	L302P (6)	—	
NP	*SMPD1*	GM13205	P330fs (6)	—	
NP	*SMPD1*	GM16193	R496L (6)	DelR608 (5)	Gaucher N370S (5)
TSD	*Hex A*	GM03461	G269S (6)	IVS12(+1)G>C (6)	
TSD	*Hex A*	GM03770	G269S (6)	1278insTATC (6)	
TSD	*Hex A*	GM11852	1278insTATC (6)	1278insTATC (6)	
TSD	*Hex A*	GM09787	IVS9+1G>A (4)	—	
TSD	*Hex A*	GM04863	1278insTATC (4)	R247W (4)	Gaucher N370S (3)

*Number of labs that detected the mutation = Number of labs that tested for the mutation.
†Mutations identified unexpectedly during characterization study.
‡Allele not detected by one LDT, but detected by the same lab using the xTAG reagent.
− indicates no mutation detected.

Diagnostics (Austin, TX). The multiplexed xTAG assay detects all disorders included in this study except GSD. GSD mutations were assayed by three laboratories in this study using LDTs.

Two laboratories used PCR-based LDTs. One of these (LDT1) tested for BS, CD, FA, FD, GD, MLIV, NP, TSD, and GSD using previously described methods (Table 3).[10] This laboratory assayed for BS, FA, and FD mutations using the Promega ReadIT SNP Genotyping System (Promega Incorporated, Madison, WI). MLIV mutations were assayed using real-time PCR on an ABI7900 (Applied Biosystems, Foster City CA), and CD, GD, NP, TSD, and GSD assays were preformed using SnapShot kits (Applied Biosystems Incorporated, Foster City, CA).

The other laboratory (LDT2, Table 3) used a pooled allele-specific oligonucleotide (ASO) hybridization assay that detects mutations for 6 of the diseases (BS, CD, FA, GD, NP, and TSD). The amplified PCR products were individually immobilized on a positively charged nylon membrane and hybridized with groups of P^{33} ASO probes. Mutation identification of pool-positive samples was made by individual ASO hybridization to normal and mutant alleles. This laboratory tested for mutations that cause FD, MLIV, and GSD with 5′ nuclease Taqman assays using real-time PCR and an allelic discrimination strategy.

One laboratory (LDT 3, Table 3) used an LDT for GSD. In this assay, multiplex PCR using universal primer sequence–tagged primers was performed as previously described.[27] Mutations were detected using allele specific oligonucleotide hybridization.[28]

Three of the laboratories used an xTAG-reagent based assay and the fourth laboratory used a PCR-based LDT to test the Batch 2 samples.

Results

We surveyed the laboratories listed on the Genetests website (*http://www.genetests.org*, last accessed April 10, 2009) and consulted with clinical laboratory directors to identify which disorders and mutations are commonly offered in AJ test panels. We found a wide variation in the disorders and alleles included in the AJ test panels offered by various clinical laboratories (Table 1). Most laboratories offer tests for BS, CD, FA, FD, GD, MLIV, NP, and TSD. A few also offer tests for GSD and maple syrup urine disease.

The alleles represented in these panels also varied, but generally included the common disease-causing alleles together with some alleles present at lower frequencies in the AJ or non-Jewish populations. For example,

Table 3. Alleles Identified by Assay Method

Disorder	Allele	xTAG assay	LDT 1†	LDT 2†	LDT 3† GSD only
BS	2281del6/ins7	+	+	+	
CD	E285A	+	+	+	
CD	A305E	+	NT	+	
CD	Y231X	+	+	+	
CD	433(−2)A>G (IVS2-2)	ND	ND	ND	
FA	IVS4(+4)A>T	+	+	+	
FA	322delG	+	NT	NT	
FD	IVS20+6T>C (2507+6T>C)	+	+	+	
FD	R696P	ND	ND	ND	
GD	N370S	+	+	+	
GD	84GG (1035insG)	+	+	+	
GD	L444P	+	+	+	
GD	IVS2+1G>A	+	NT	+	
GD	R496H	ND	NT	ND	
GD	D409H	ND	NT	NT	
GD	V394L	+	NT	NT	
GD	del55bp	ND	NT	NT	
MLIV	IVS3-2A>G	+	+	+	
MLIV	del6434(ex1-7)	+	+	+	
NP	R496L	+	+	+	
NP	fsP330	+	+	+	
NP	L302P	+	+	+	
NP	delR608	+	+	NT	
TSD	1278+TATC	+	+	+	
TSD	IVS12+1G>C	+	+	+	
TSD	G269S	+	+	+	
TSD	IVS9(+1)G>A	+	NT	+	
TSD	R247W	+	NT	+	
TSD	R249W	ND	NT	ND	
TSD	Del7.6kb	ND	NT	ND	
TSD	IVS7+1G>A	ND	NT	ND	
GSD	R83C	NT	+	+	+
GSD	Q347X	NT	+	+	+

LDT, laboratory - developed test; NT, allele not included in assay, or not tested; ND, allele included in assay but not detected in samples.
†Assay performed by one laboratory.
+Allele detected.

three TSD mutations, 1278insTATC, IVS12(+1)G>C, and G269S account for over 98% of mutant alleles in the AJ population. Testing for IVS9(+1)G>A and the 7.6-kb deletion is often included to increase the detection rate in the non-AJ population.[6] In addition, the R247W and R249W alleles are commonly tested to clarify abnormal enzyme test results due to the presence of these pseudodeficiency alleles. Inclusion of the A305E mutation in CD panels and delta R608 in NP mutation panels considerably increases the detection rate in the non AJ population.[6]

Thirty-one cell lines were chosen from the NIGMS Cell Repository at the Coriell Cell Repositories to create an AJ RM panel. The selected lines represent alleles included in laboratory test panels for the nine disorders. Compound heterozygotes and homozygous genotypes were selected.

Six clinical genetic laboratories volunteered to characterize these materials using their current assay method. Three to six laboratories (depending on their test panels, Table 3) independently tested DNA prepared from the 31 cell lines for 33 different disease alleles. Twenty-five different alleles were identified in the samples (Table 2). Alleles not detected in any sample are present at very low frequencies in affected populations (Table 1). All laboratories were able to detect the presence of every allele included in their assay that was present in the samples. One laboratory was unable to detect the L444P allele in DNA sample NA04394 using their LDT, but was able to detect it in sample GM08752. This laboratory, which no longer uses the LDT, was subsequently able to detect L444P in this sample with the xTAG assay. It is likely that the L444P allele in sample NA04394 represents a GBA pseudogene recombinant that interfered with this assay result.[29] There were no other discrepant results.

Discussion

This study describes the characterization of 31 genomic DNA reference materials for AJ genetic testing. These materials were selected to include heterozygous (simple and compound) and homozygous genotypes for the nine disorders (BS, CD, FA, FD, GD, MLIV, NP, TSD, and GSD) commonly included on clinical AJ testing panels.

A group of six commercial and academic molecular diagnostic laboratories volunteered to test these samples using their own AJ panel assays. This arrangement allowed each of the 31 genomic DNA samples to be independently tested in three to six laboratories for 33 different alleles on a variety of test platforms.

We identified 25 different alleles in these samples (Table 2). With one exception, there were no discordant results indicating that the samples will function in a variety of assay types, including a commonly used commercial platform. All laboratories were able to confirm the expected genotype of each DNA sample. In addition, since the testing laboratories were blinded to the expected genotypes, each sample was tested for all disorders and alleles included in the laboratory's panel. This allowed us to identify an unanticipated GD mutation in three of the samples (NA02528, NA16193, and NA04863).

Although genomic DNA samples containing most of the mutations commonly included in AJ testing panels were characterized in this study and are available from Coriell, there are a number of mutations included in these panels that are not publicly available as either genomic DNA from Coriell or from other sources. These include the R696P well as the 433(−2)A>G mutations that cause FD and CD respectively (Table 1). The GeT-RM program will work with Coriell and patient communities to create cell lines and genomic DNA materials to satisfy these unmet needs.

The quality assurance of molecular genetic testing in the United States is mandated by a number of regulations and guidelines.[30] Current Clinical Laboratory Improvement Amendment regulations (Code of Federal Regulations. The Clinical Laboratory Improvement Amendments [CLIA] 42 CFR Part 493. [1256], *http://www.access.gpo.gov/nara/cfr/waisidx_03/42cfr493_03.html*, last accessed November 18, 2008), as well as New York (New York State Clinical Laboratory Evaluation Program Laboratory Stan-

dards, *http://www.wadsworth.org/labcert/clep/clep.html*, last accessed November 18, 2008) and Washington State (Washington State Medical Test Site Rules [Chapter 246-338 WAC], *http://apps.leg.wa.gov/WAC/default.aspx?cite=246-338*, last accessed November 18, 2008), regulations and recommendations by numerous professional societies (American College of Medical Genetics Standards and Guidelines for Clinical Genetic Laboratories, *http://www.acmg.net/Pages/ACMG_Activities/stds-2002/g.htm*, last accessed Nov 18, 2008),[31–33] contain general quality assurance and QC requirements for genetic testing. These requirements describe the daily use of both positive and negative controls to monitor the ability of the assay to correctly identify mutations present in patient samples. In addition, some guidelines suggest that for multiplex tests, controls be rotated to include all mutations assayed. (American College of Medical Genetics Technical Standards and Guidelines for CFTR Mutation Testing 2006, *http://www.acmg.net/Pages/ACMG_Activities/stds-2002/cf.htm*, last accessed March 10, 2009) The American College of Medical Genetics has developed a Technical Standard and Guideline for Ashkenazi Jewish Testing that provides guidance on testing and quality assurance for AJ disorders.[6]

The lack of available QC and RMs for genetic testing has been recognized as a critical need of the genetic testing community (Centers for Disease Control and Prevention, *http://www.cdc.gov/dls/pdf/genetics/dyncor.pdf*, last accessed January 9, 2009).[34,35] For the majority of genetic tests, no characterized DNA or cell lines that can be used as RMs for QC, proficiency testing/external quality assessment, genetic test development/validation, or research are publicly available. In the absence of such material, clinical laboratories and test developers use residual patient specimens, when available, or make oligonucleotides for this purpose. The lack of such materials also affects the ability of proficiency testing/external quality assessment providers to produce sufficient and varied challenges.

Cell repositories that provide genomic DNA and/or cell lines containing mutations are the only publicly available sources of DNA for RMs for most tests.[30,34,35] Coriell's NIGMS Human Genetic Cell Repository offers a vast array of cell lines and DNA products. However, the submissions to Coriell are voluntary and the associated information is often limited and uncorroborated. Many clinical genetic testing laboratories routinely use cell lines and DNA from the repository as positive and negative controls after characterizing them in their assay. Some companies have developed synthetic multiplex DNA controls that contain multiple mutations for a few genetic disorders, including one for the AJ Panel disorders and one company offers genomic DNA controls for pharmacogenetic assays.

To address these quality assurance needs, the GeT-RM, together with the genetic testing community and the Coriell Cell Repositories, has established a process to develop characterized genomic DNA materials for use as RMs for genetic testing. The materials being developed are intended to serve as RMs for daily use. These materials differ from standard reference materials or certified reference materials,[30,36] which are more highly characterized and expensive and are intended for more occasional use such as assay calibration and/or assay validation.

The RMs developed by this project may be used for proficiency testing, quality control, assay development/validation, or research applications and are publicly available from Coriell's NIGMS Human Genetic Cell Repository(*http://ccr.coriell.org/Sections/Collections/NIGMS/?Ssid=8,* last accessed April 10, 2009). The availability of these characterized RMs should help to ensure the quality and accuracy of AJ panel genetic testing.

Information about these and other available RM and QC materials is presented on the GeT-RM program website; *http://www.cdc.gov/dls/genetics/rmmaterials/default.aspx* (last accessed April 10, 2009).

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