Developmental Delay Algorithm

Mountain States
REGIONAL GENETICS NETWORK
Utah Team

Confirm Suspected Developmental Delay
Refer Patient for Early Intervention
Get on Genetics' Schedule
Follow Algorithm

Regression or Neurologic Abnormalities
(e.g., seizures, macro- or micro-cephaly)

Non-specific Presentation

NEUROLOGY REFERAL

Brain MRI with Spectroscopy

No Findings, Reflex to Genetic Testing

GENETIC TESTING

Tier 1 Testing
Chromosomal MicroArray
Fragile X Trinucleotide

Tier 2 Testing
Developmental Delay Panel
Parental Genetic Testing

Tier 3 Testing
Metabolic Testing

Findings

Findings

CONFIRMATORY TESTING

with Genetics/Neurology support

DIAGNOSIS ESTABLISHED

- Advise family; provide educational materials
- Establish medical home
- Refer to relevant specialists

NO FINDINGS

- Keep Genetics Appointment
- Discuss Case with Genetics/Neurology as needed
- Advise family; provide educational materials
- Establish medical home
- Refer to relevant specialists

Utah Support Team

Pediatric Neurology - 801-587-7575 | Mike Lloyd | Michael.Lloyd@hsc.utah.edu
Metabolic Genetics - 801-585-2457 | Nicola Longo | Nicola.Longo@hsc.utah.edu
Genetic Counselor / Labs Ordering - 801-584-8256 | Mary Rindler | MRindler@utah.gov
Administrative / Materials - 801-584-8256 | Heidi Wallis | HeidiWallis@utah.gov
Program Feedback - 801-581-2205 | Chuck Norlin | Chuck.Norlin@hsc.utah.edu

www.mountainstatesgenetics.org/projects/current-projects/developmentaldelay

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REGIONAL GENETICS NETWORK
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Note: Benefits are dependent on the plan chosen by the participant. It is recommended that individuals call to confirm coverage of testing. There is no guarantee of payment.

Insurance Plans	*In-Network Labs*
Aetna	Standard Aetna Network – In-Network for the U Out of Network for IHC Ambry Genetics GeneDX Quest Diagnostics
Cigna Genetic Counseling may be required	PPO/HMO – In-Network for the U In-Network IHC Ambry Genetics ARUP Laboratories GeneDX Labcorp Quest Diagnostics
Medicaid	No contract required for the U No contract required for IHC Invitae accepts Medicaid for pediatric microarray, FISH, karyotype and Fragile X Labcorp GeneDX – requires prior authorization
PEHP	Plan dependent for hospital Labcorp Quest Diagnostics PAML
Regence BCBS	In-network for the U Out of Network for IHC Labcorp Quest Diagnostics
Select Health	Out of network for the U In-Network for IHC Ambry Genetics Labcorp Invitae
Tricare	Tricare for Life and Tricare for West In-network for the U No contract required for IHC Labcorp
United Healthcare	In-Network for the U In-Network for IHC Ambry Genetics ARUP laboratories GeneDX Labcorp

Laboratories

Ambry Genetics

https://www.ambrygen.com/
Client Services (949) 900-5500
*Genetic Counselors on staff
Insurance Verification (949) 900-5794
Kit Request: https://www.ambrygen.com/clinician/order-sample-kit

Financial Assistance:

- Estimate your payment
- Gratis testing for any patient at or below the federal poverty line
- 100-600% FPL eligible for an OOP reduction
- Competitively-priced cash pay price
- Pre-verify your insurance benefits
- Patient Portal

Test Name	Test Codes	Sample Type	TAT	CPT Codes
SNP Array	5490	Blood, Saliva, Saliva Swab	14-21 days	
Fragile X-Associated Disorders	4544	Blood, Saliva, Saliva Swab	7-14 days	
Neurodevelopment – Expanded (196 gene panel)	7028	Blood, Saliva, Saliva Swab	4-6 weeks	
AutismNext (48 gene panel)	7024	Blood, Saliva, Saliva Swab	14-21 days	
IDNext (140 gene panel)	7027	Blood, Saliva, Saliva Swab	14-21 days	

Requisitions:

SNP Array

- https://www.ambrygen.com/file/material/view/904/ClinicalGenomics_TRF_0718_final.pdf

Neurology Test

- https://www.ambrygen.com/file/material/view/905/Neuro_TRF_0718_final.pdf

Consent Form:

- https://www.ambrygen.com/file/material/view/425/General_Consent_Form_0718_Final.pdf

Letters of Medical Necessity:

- https://www.ambrygen.com/clinician/forms#letter-of-medical-necessity

**Saliva Swab available only for Fragile X and SNP array

ARUP Laboratories

https://www.aruplab.com/
Genetic Processing (800) 242-2787 x 3301
Client Services (800) 522-2787

Does not do third party billing
Intermountain Healthcare and UUHSC will automatically send SNP array and Fragile X testing to ARUP Laboratories

Test Name	Test Codes	Sample Type	TAT	CPT Codes
Cytogenomic SNP Array	2003414 2006267	Blood Buccal Swab	10-14 days	81229
Fragile X (FMR1) with Reflex to Methylation Analysis	200933	Blood	4-14 days	81243, reflexed add 81244
Autism and Intellectual Disability Comprehensive Panel (testing includes SNP Array, Fragile X, Plasma Amino Acids, Plasma Acylcarnitines, Urine Organic Acids, MPS Screen, Creatine Disorders Panel)	2014314	4 specimens required: Urine, Plasma, 2 whole blood	5-18 days	82017, 82664, 83864, 83918, 82540 x2, 82542 x2, 82570, 82139, 81229, 81243, reflexed add 81244
Autism and Intellectual Disability Metabolic Panel (testing includes Plasma Amino Acids, Plasma Acylcarnitines, Urine Organic Acids, MPS Screen, Creatine Disorders Panel)	2014312	Urine, Plasma	5-18 days	82017, 82664, 83864, 83918, 82540 x2, 82542 x2, 82570, 82139

Patient history forms:
Cytogenomic SNP Array: http://ltd.aruplab.com/Tests/Pdf/76
Autism and Intellectual Panels: http://ltd.aruplab.com/Tests/Pdf/64

GeneDX

https://www.genedx.com/
Client Services: 888-729-1206
*Genetic Counselors on staff
Insurance Billing: 855-519-2100
Kit request: https://www.genedx.com/test-catalog/supplies/#!/supplies-list

Insurance: GeneDx accepts all commercial insurance policies. The patient is responsible for only the co-pay, co-insurance and unmet deductible dictated by his or her insurance carrier. Based on the patient's insurance, GeneDx will perform a benefits investigation (BI) to estimate the patient's out-of-pocket cost. GeneDx will attempt to contact the patient if the patient's estimated out-of-pocket cost is expected to be greater than $100.
Institutional billing: ARUP Laboratory is contracted to send to GeneDX

Test Name	Test Codes	Sample Type	TAT	CPT Codes
Chromosomal Microarray	910	Blood, Saliva Swab	3 weeks	81229
FMR1 CGG Repeat Analysis	522	Blood, Saliva Swab	2 weeks	81243
Autism/ID Panel	T395	Blood, Saliva Swab	4 weeks	81302, 81321, 81323, 81404, 81405, 81406, 81407, 84108
Autism/ID Xpanded Panel	952	Blood, Saliva Swab	6 weeks	81470, 81471

Requisition form:

- https://www.genedx.com/wp-content/uploads/crm_docs/67559-Neurology-test-req-new-fornat-var.pdf

Medical Necessity Template available on-line

- https://www.genedx.com/all-forms/

Cigna and United Healthcare may require a genetic counseling form

- https://www.genedx.com/wp-content/uploads/2019/02/200646_GDX-GC-Referral-form-Interactive4.pdf

Invitae

https://www.invitae.com/en/
Clinical Consult Services (800) 436-3037
*Genetic Counselors on staff
Kit Request: https://www.invitae.com/request-a-kit/#/

Developmental Disorders – Chromosomal Microarray and Fragile X
Requisition:
Microarray and Fragile X

- http://marketing.invitae.com/acton/attachment/7098/f-0983/1/-/-/-/-/12112017

Insurance billing (US only) ***Taken from Invitae's website**
Invitae will contact the patient's insurance company directly to coordinate coverage and payment. Patients do not need to contact their insurance company to find out if testing is covered or to obtain reimbursement.

Invitae is proud to be in-network for more than 250 million patients in the United States—and growing. But no matter a patient's in-network or out-of-network status, Invitae is committed to making genetic testing affordable for everyone.

If your patient receives a bill for more than $100, please have your patient call us to discuss payment options. We offer programs to help those few patients with higher out-of-pocket costs, including interest-free payment plans and financial assistance.

Please be prepared to provide the following information if you wish to bill insurance for an order:

- The patient's first and last name, phone number, and mailing address
- A copy (front and back) of the patient's insurance card
- Relevant ICD-10 codes
- A letter of medical necessity
- Any applicable precertification forms, available on the Forms page

Patients may receive an explanation of benefits (EOB) from their insurance company in the mail. This is not a bill. Invitae will also receive this EOB and will handle any appeals processes.

Labcorp

https://www.labcorp.com/
Genetic Counseling Services (800) 345-4363
Telegenetics (800) 245-4363

Test Name	Test Codes	Sample Type	TAT	CPT Codes
SNP Array – Pediatric (Reveal)	510002	Blood, Buccal swab	14-21 days	81229
Fragile X, PCR and Southern Blot Analysis	511655	Whole Blood		81243, 81244

SNP Array Clinical Questionnaire: https://www.labcorp.com/tests/related-documents/rep_443
SNP Array Eligibility/Prior Authorization: https://www.labcorp.com/tests/related-documents/L13380

Lineagen

https://lineagen.com/home/
Client Services: 801-931-6200
Genetic Counselor: 801-931-6191
Insurance Billing: 855-519-2100
Kit request: https://lineagen.com/about/#contact

Insurance: Personalized insurance assistance includes:

- Lineagen handles all insurance correspondence, from pre-authorizations to appeals
- Expert team of insurance specialists with years of experience and success at dealing with thousands of claims
- Various financial assistance such as Lineagen Care Program, payment plans and other assistance options

Test Name	Test Codes	Sample Type	TAT	CPT Codes
FirstStep PLUS Optimized Chromosomal Microarray		Saliva		81229
Fragile X Syndrome Testing		Saliva		81243, reflex to 81244 if needed

Requisition and Consent form:

- https://lineagen.app.box.com/v/fsdx-plus-test-req

GENETIC TESTING PRIOR AUTHORIZATION REQUEST FORM

DO NOT USE THIS FORM FOR HEALTH CHOICE UTAH, MOLINA, HEALTHY U OR SELECT HEALTH REQUESTS

MEMBER INFORMATION

MEMBER NAME:	FAX THIS COMPLETED FORM AND ALL REQUIRED SUPPORTING DOCUMENTATION TO:
MEMBER ID #:	(801) 536-0958
DOB: / AGE:	OR MAIL TO:
DATE: / DATE(S) OF SERVICE REQUESTED:	PO BOX 143111 SALT LAKE CITY, UT 84114-3111
IS THIS A RETROACTIVE REQUEST? ◯ YES ◯ NO (If yes, reason for retroactive request is required) _____	FOR QUESTIONS REGARDING GENETIC TESTING PRIOR AUTHORIZATONS, PLEASE CALL: (801) 538-6155 OPTIONS 3, 3, 1
NUMBER OF PAGES INCLUDED WITH REQUEST: _____	

PROVIDER INFORMATION

NAME, ADDRESS AND NPI # FOR REQUESTING PROVIDER	NAME, ADDRESS AND NPI # FOR LABORATORY
Name: _____	Name: _____
Address: _____	Address: _____
_____	_____
Phone: (____) _____ Fax: (____) _____	Phone: (____) _____ Fax: (____) _____
Contact Name: _____	Contact Name: _____
NPI #: _____	NPI #: _____

REQUIRED CLINICAL INFORMATION

ICD-10 CM CODE(S):	DIAGNOSIS CODE DESCRIPTION
1)	
2)	
3)	
HCPCS CODE:	HCPCS CODE DESCRIPTION
1)	
2)	
3)	
GENE(S) TO BE TESTED (IF NOT IDENTIFIED WITH HCPCS CODE):	

TYPE OF TEST(S) (E.G., Mutation panel, Full gene sequencing, Gene panel, DEL/DUP):
DESCRIBE THE CLINICAL VALIDITY OF THE TEST(S) (e.g. analytic validity, sensitivity, specificity, positive and negative predictive value):
DESCRIBE THE CLINICAL UTILITY:
DOES THE PATIENT EXHIBIT CLINICAL/PHYSICAL FEATURES ASSOCIATED WITH THE MUTATION IN QUESTION? ◯ YES ◯ NO IF YES, PLEASE SPECIFY:
RELEVANT FAMILY HISTORY:
DESCRIBE CLINICAL FINDINGS FOR THIS PATIENT:
DESCRIBE PAST TREATMENTS THAT HAVE BEEN PROVIDED:
DESCRIBE PREVIOUS TEST RESULTS THAT SUPPORT NEED FOR THIS GENETIC TEST:
DESCRIBE CURRENT TREATMENT PLAN:

HOW WILL KNOWLEDGE OF THE PRESENCE OF THE GENETIC DEFECT CHANGE THE CURRENT TREATMENT AND WHY:

Medical Management:

Medical Interventions:

Monitoring and Screening:

Medication Management:

Other:

PHYSICIAN SIGNATURE: _____ DATE: _____

ARUP LABORATORIES | www.aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: (801) 583-2787, toll free: (800) 522-2787
Julio C. Delgado, MD, MS, Director of Laboratories

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/25/2018
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	

Cytogenomic SNP Microarray

ARUP test code 2003414

Cytogenomic SNP Microarray

Normal (Ref Interval: Normal)

Specimen Received
Specimen Type: Peripheral Blood
Reason for Referral: Vascular ring, Double aortic arch, Atretic left distal segment, Narrowed trachea
Test Performed: CMA SNP

NORMAL MICROARRAY RESULT

Genetic results
ISCN: arr(1-22)x2,(XY)x1 (hg19) (normal male result)

The cytogenomic microarray analysis indicated no clinically significant abnormalities and is consistent with a male chromosome complement.

Recommendation:
Genetic counseling

Certain copy number variants (CNV) have been observed in many individuals with no phenotypic associations and are believed to be clinically insignificant. Any such CNVs which have been detected in this patient are thus not specifically listed in this report.

If you would like additional information, please contact an ARUP genetic counselor at (800) 242-2787 extension 2141. ARUP genetic counselors are available to help health care providers with test selection, result interpretation and identifying local clinical genetic services.

Chromosomal microarray analysis (CMA) was performed using Affymetrix CytoScan HD microarray. This microarray consists of 2,696,550 oligonucleotide probes across the genome, including 1,953,246 unique non-polymorphic probes, and 743,304 SNP (single nucleotide polymorphism) probes. These SNP probes allow for the identification of long contiguous stretches of homozygosity (LCSH) that may suggest uniparental disomy (UPD), or regions of the genome identical by descent. Patient hybridization parameters are compared to data derived from 100 individuals with normal microarray results. Deletions smaller than 50 kb and duplications smaller than 400 kb may not be reviewed. Detected copy number variations (CNVs) are reported when found to have clear or suspected clinical relevance; CNVs devoid of relevant gene content or reported as common findings in the general population may not be reported. Regions of homozygosity are reported when a single LCSH is greater than 8-15 Mb (dependent upon chromosomal location and likelihood of imprinting disorder), or when the total autosomal LCSH proportion is greater than 3 percent (only autosomal LCSH greater than 3 Mb are considered for this estimate). Genomic linear positions are

	given relative to NCBI build 37 (hg19). This microarray and associated software (Chromosome Analysis Suite) are manufactured by Affymetrix and used by ARUP Laboratories for the purpose of identifying DNA copy number gains and losses associated with large chromosomal imbalances. This analysis will not detect all forms of polyploidy, balanced rearrangements (eg. inversions and balanced chromosomal translocations), small deletions, point mutations, and some mosaic conditions. While this assay has been extensively validated by ARUP Laboratories and other clinical laboratories per ACMG guidelines, it is not feasible to validate every potential genomic imbalance in the human genome. Furthermore, this technique only identifies the regions of imbalance; it does not provide information regarding the arrangement or mechanisms responsible. For these reasons, we may recommend that some chromosomal microarray results be characterized by fluorescence in situ hybridization (FISH) or standard chromosome analysis. As a member of the Clinical Genome Resource (ClinGen), ARUP Genomic Microarray Laboratory submits clinical information and test results to a HIPAA-compliant, de-identified public database as part of the National Center for Biotechnology's (NCBI) effort to improve diagnostic testing and our understanding of the relationships between genetic changes and clinical symptoms. For more information about the database, called ClinVar, see ARUP's website at www.aruplab.com/genetics. Confidentiality of each sample is maintained. To learn more about ClinGen, log onto www.clinicalgenome.org. If you do not want your results to be submitted to the ClinVar database, you can choose not to participate (opt-out). If you opt-out, your microarray test and test results will not be affected. To opt-out, call ARUP Laboratories Genetics Processing at (800) 242-2787 ext. 3301 to request that your test results not be sent to ClinVar. This result has been reviewed and approved by Erica F. Andersen, Ph.D., FACMG Electronic Signature INTERPRETIVE INFORMATION: CYTOGENOMIC SNP MICROARRAY Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS
EER Cytogenomic SNP Microarray	EERUnavailable

H=High, L=Low, *=Abnormal, C=Critical

ARUP LABORATORIES | www.aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: (801) 583-2787, toll free: (800) 522-2787
Julio C. Delgado, MD, MS, Director of Laboratories

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/7/1991
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Fragile X (FMR1) with Reflex to Methylation Analysis

ARUP test code 2009033

FRAG X Specimen	Whole Blood
Fragile X Allele 1	30 CGG repeats
Fragile X Allele 2	30 CGG repeats Presumed Homozygous
Fragile X Methylation Pattern	Not Applicable
Fragile X Interpretation	See Note Negative: This individual has two normal alleles; therefore, she is not a Fragile X carrier. This test does not detect rare mutations in less than 1% of Fragile X cases. This result has been reviewed and approved by Yuan Ji, Ph.D.

H=High, L=Low, *=Abnormal, C=Critical

ARUP LABORATORIES | www.aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: (801) 583-2787, toll free: (800) 522-2787
Julio C. Delgado, MD, MS, Director of Laboratories

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	5/6/2018
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	

Cytogenomic SNP Microarray

ARUP test code 2003414

Cytogenomic SNP Microarray — **Abnormal** * (Ref Interval: Normal)

```
Specimen Received
Specimen Type: Peripheral Blood
Reason for Referral: Double outlet right ventricle
Test Performed: CMA SNP
------------------------------------------------------------
ABNORMAL MICROARRAY RESULT

22q11.2/DiGeorge/Velocardiofacial Syndrome Deletion

Copy number change: 22q11.21 loss
Base pair coordinates: 18,916,827-21,465,659 (hg build 19)
Approximate Size: 2.5 Mb

Sex chromosome complement: XY (male)

Genetic results:
ISCN: arr[hg19] 22q11.21(18,916,827-21,465,659)x1

The cytogenomic microarray analysis showed an interstitial
deletion involving chromosome 22 (2.5 Mb deleted) within
22q11.21, indicating monosomy for this region.

This is a deletion of the 22q11.2/DiGeorge/Velocardiofacial
syndrome region involving recurrent low-copy repeat (LCR)
regions A and D. The reported size of this deletion may vary
across studies due to flanking segmental duplication
architecture. This region contains 66 genes (listed below),
including the gene TBX1, a critical gene within the region.

Clinical features associated with the
22q11.2/DiGeorge/Velocardiofacial syndrome deletion are variable
and may include: conotruncal cardiac anomalies, palatal
anomalies, immune dysfunction, hypocalcemia, developmental
delay, learning disabilities, behavioral problems,
characteristic facial features, and other minor features (see
References).

The following resources may be useful for patient and family
member education and support: The International 22q11.2
Foundation (www.22q.org) and The Unique Rare Chromosome Disorder
Support Group (www.rarechromo.org).

As up to 10% of these deletions are inherited, parental FISH
testing may be considered.

Recommendations:
1. Genetic counseling.
2. As some individuals with this 22q11.21 deletion might be
mildly affected or apparently healthy, examination of parents by
FISH may be considered to determine if a parent also carries
```

H=High, L=Low, *=Abnormal, C=Critical

DISEASES *Overview of 81 diseases presented in 15 biochemical categories*

- Amino Acids
- Cholesterol & Bile Acids
- Creatine
- Glucose Transport & Regulation
- Fatty Aldehydes
- Hyperhomocysteine
- Lysosomes
- Metals
- Mitochondria
- Neurotransmission
- Organic Acids
- Peroxisomes
- Pyrimidines
- Urea Cycle
- Vitamins/Co-Factors

Diagnosis of Pediatric Developmental Delay

What is Developmental Delay?

- A child younger than 5 years old has global developmental delay (GDD) when they perform at least 2 standard deviations below the norm in two or more developmental categories. GDD is prevalent in 1-3% of children younger than 5 years. [1]
- Studies suggest that underlying genetic issues account for anywhere between 17-50% of developmental delay cases. Other biological and social factors may also cause developmental delay.[2]

How is Developmental Delay Diagnosed?

- Per AAP guidelines, developmental **surveillance** should be performed at every pediatric wellness exam (except for 9 month, 18 month, and 30 month appointments when developmental **screening** should be performed, see below). [3]
    - There are five components of surveillance: [4]
        1. Asking parents if they have any concerns about their child's development
        2. Maintaining a history of the child's development
        3. Observing the child
        4. Identifying risk factors
        5. Recording the findings of the above components
    - The CDC provides a checklist in paper and app form of developmental milestones for children aged 2 months to 5 years old. These checklists include activities that a child should be able to perform at the appropriate age, and can be used by parents and physicians as a way to monitor a child's development.[5]
- Developmental **screening** should be performed at the 9 month, 18 month, and 30 month appointments. Screening should be performed more often as concerns arise among parents and physicians, especially as a consequence of missed milestones recognized during developmental surveillance. [3, 4]
    - There are multiple tests that can be used for developmental screening, most of which are parent administered and reviewed by a physician. These are **not diagnostic,** but rather identify specific areas of underperformance in various developmental areas for a specific age. The following tests are suggested:
        1. Ages and Stages Questionnaire[6,7]
            - Administered by parents
            - Takes 10-15 minutes to test and 2-3 minutes to be evaluated by a physician
            - Can be performed online or on paper, and can be done anywhere
        2. Parents' Evaluation of Developmental Status (PEDS)[6,8]
            - Administered by parents
            - 2-10 minute administration
            - Can be performed online or in print, can be done anywhere
            - Reviewed by a physician
        3. Denver II- Developmental Screening Test[4]
            - Administered by a physician
            - 10-20 minute administration

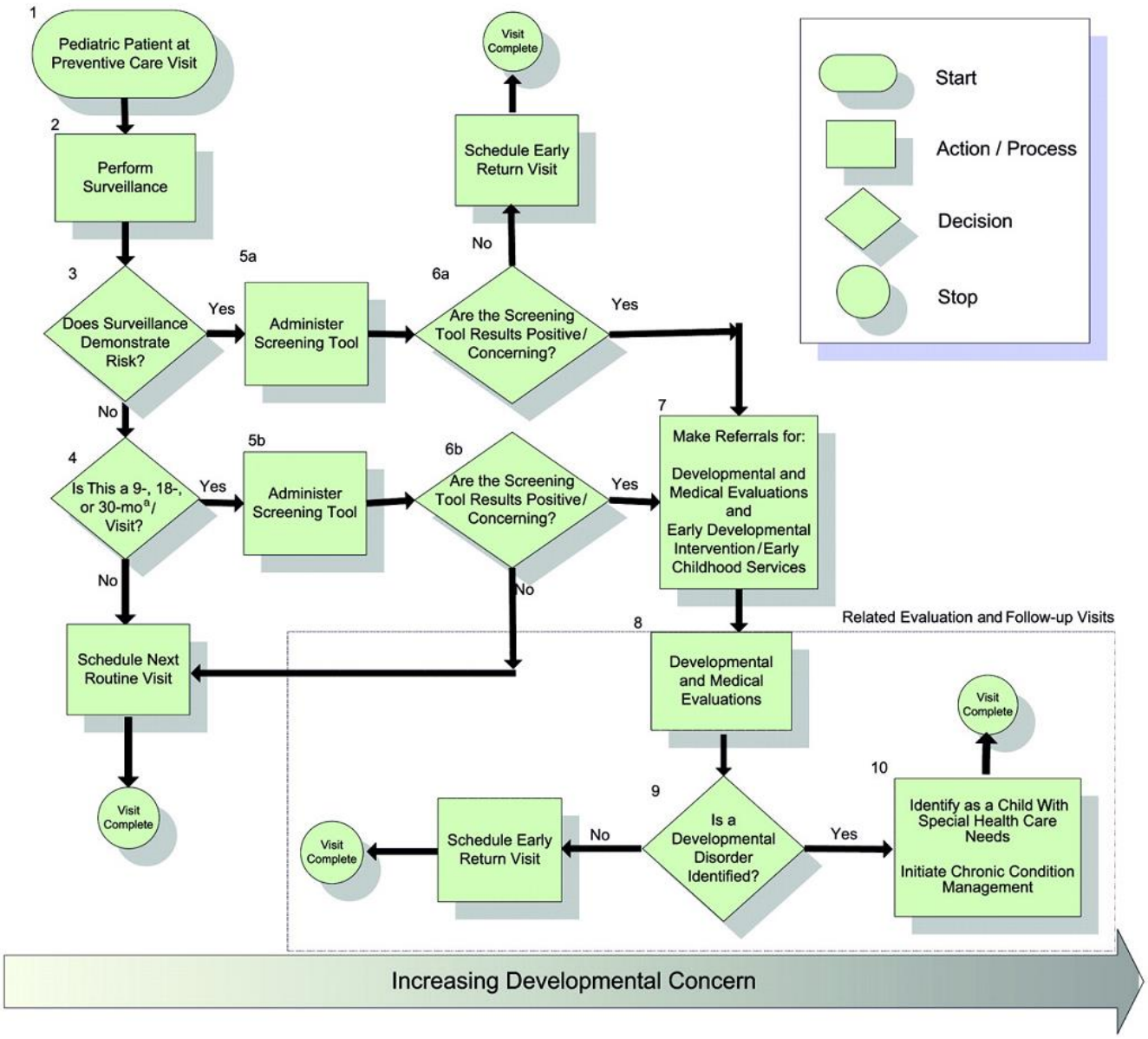
If a Child Has Concerning Developmental Screening Results:

- MCHAT, a screening test for Autism can be performed.
- All AAP guidelines (including hearing tests) should be followed.
- The child must be referred to the Early Childhood Intervention Program where diagnostic tests will be performed to determine if a child has developmental delay. They can also be referred to a Developmental Pediatrician.[4,9]

After Developmental Delay Diagnosis

- Following diagnosis, the physician should review biological and social risk factors. These should be reviewed and addressed before moving on to genetic tests that could identify underlying genetic causes for developmental delay. The child can be referred to ABA or other appropriate therapy before their genetics appointment.

Diagnosis of Developmental Delay AAP[4]



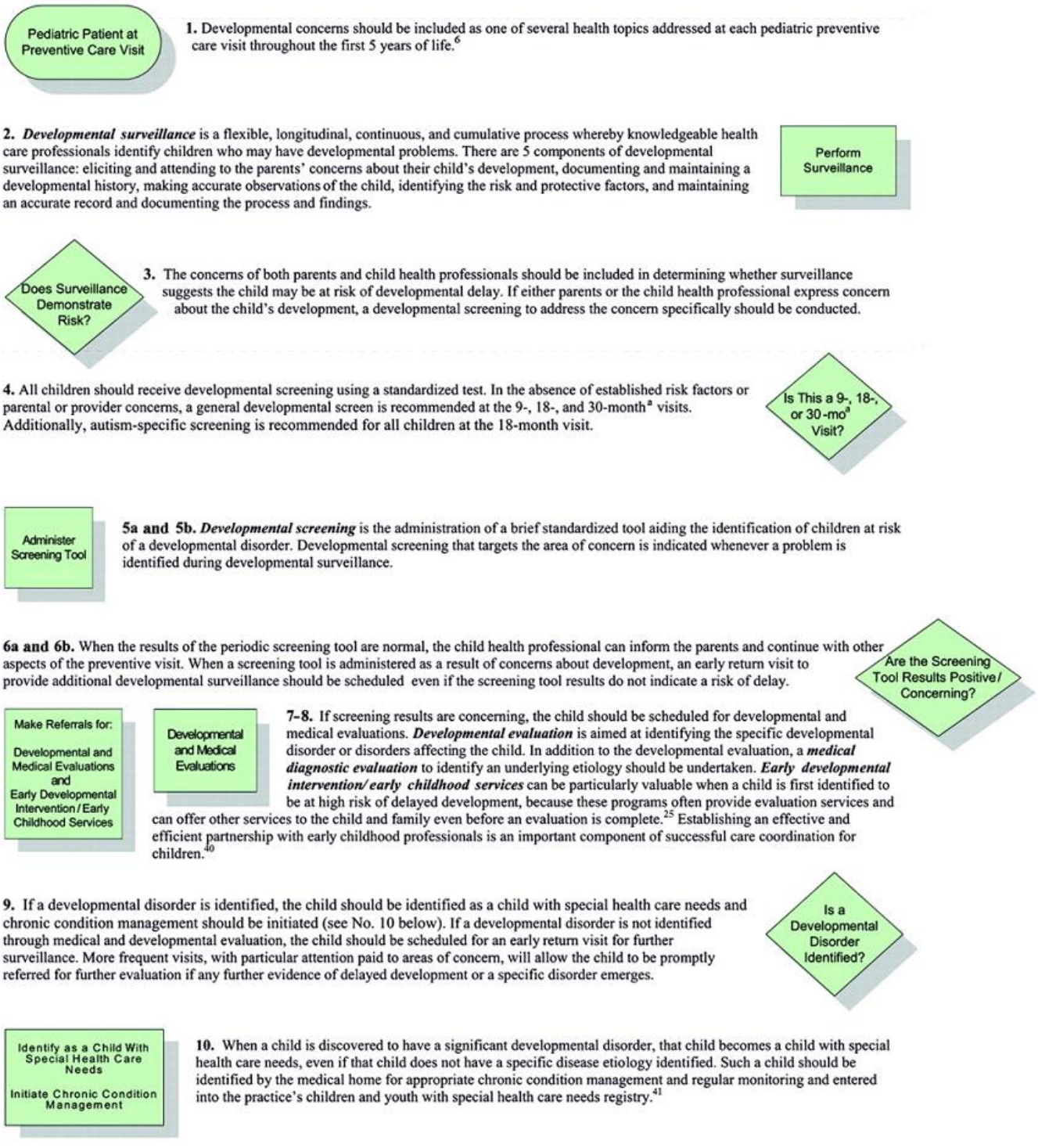


FIGURE 1
Developmental surveillance and screening algorithm within a pediatric preventive care visit. [a] Because the 30-month visit is not yet a part of the preventive care system and is often not reimbursable by third-party payers at this time, developmental screening can be performed at 24 months of age.

[1] "Global Developmental Delay Evaluation: Evidence-based Approach." The University of Chicago. Accessed June 4, 2018. https://pedclerk.bsd.uchicago.edu/page/global-developmental-delay-evaluation-evidence-based-approach

[2] Karam, Simone M et al. "Genetic Causes of Intellectual Disability in a Birth Cohort: A Population-Based Study. *American Journal of Medical Genetics* 167, no. 6 (2015): 1204-1214.

[3] "Recommendations for Preventative Pediatric Health Care." Bright Futures/American Academy of Pediatrics (2017).

[4] Council on Children with Disabilities. "Identifying Infants and Young Children with Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening." *Pediatrics* 118, no. 1 (2006, reaffirmed 2010 and 2014): 405-420.

[5] "Learn the Signs, Act Early: Developmental Milestones." Center for Disease Control. Accessed June 4, 2018. https://www.cdc.gov/ncbddd/actearly/milestones/index.html

[6] "Birth to 5: Watch me Thrive!: A Compendium of Screening Measures for Young Children." US Department of Health and Human Services, Washington, D.C., March 2014.

[7] "ASQ-3." Ages & Stages Questionnaires. Accessed June 4, 2018. http://agesandstages.com/products-services/asq3/

[8] "Developmental-Behavioral Screening & Evaluation." PEDS Test. Accessed June 4, 2018. http://www.pedstest.com/default.aspx

[9] "Learn the Signs, Act Early: Information for Healthcare Providers." Center for Disease Control. Accessed June 13, 2018. https://www.cdc.gov/ncbddd/actearly/hcp/index.html

Non-Genetic Causes of Developmental Delay

The PCP should obtain a comprehensive history to determine if the presence of one or more of these factors is sufficient to account for the developmental delay. A genetic cause of developmental delay may still be present in a child with one or more of these factors.

- PERINATAL FACTORS:
  - Maternal factors
    - Maternal age below 20 or above 35[1]
    - Overweight[2,3]
    - Underweight[3]
    - Preeclampsia[3]
    - Diabetes[3]
    - Autoimmune disease[3]
    - Chorioamnionitis[3]
    - Psychiatric drug use
  - Intrauterine Infection[4]
- POSTNATAL FACTORS:
  - Low birth weight[1,3,4,5]
  - Premature birth[1,3,4,5]
  - Post-term births[2]
  - Complications during birth[4]
  - Hypoxic-Ischemic encephalopathy[3]
  - Neonatal ischemic stroke[3]
  - Neonatal cerebral venous sinus thrombosis [3]
  - Neonatal sepsis[3]
  - Periventricular Leukomalacia[3]
  - Untreated jaundice[4]
  - Head injury[2]
  - Cerebral infections [2]
  - Hypothyroidism [3]
  - Intracranial hemorrhage[3]
  - Hypoglycemia[3]
  - Hypocalcemia[3]
  - Hearing loss[6]
  - Environmental toxins (lead)[4,7]
- SOCIAL FACTORS:
  - Low maternal/paternal education[1,8,5]
  - Exposure to violence, abuse[7,9]
  - Attributes associated with poverty[9]
    - Malnutrition
    - Poor housing
    - Maternal depression[7]
    - Institutionalization[7]
    - Poor stimulation[10]
    - Inadequate access to healthcare[10]

[1] Ozkan, Mehpare et. al. “The Socioeconomic and Biological Risk Factors for Developmental Delay in Early Childhood.” *European Journal of Pediatrics* 171, no.12 (December 2012):1815-21.

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Author

Grace S. Miller
Intern, Texas Health Institute

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Approach to Genetic Diagnosis in Developmental Delay

Introduction

- This document does not replace input from a clinical geneticist, but given that many regions are underserved by clinical genetics, this document may assist primary care providers in conducting an initial diagnostic evaluation.
- Patients with new-onset seizures, developmental regression, concern for increased intracranial pressure or other acute concerns should be referred to the appropriate specialty.
- This document will change over time with new developments in genetic testing.

Initial considerations

- The American Academy of Pediatrics has published their statement on appropriate genetic evaluation of children with developmental delay: see Moeschler et al Pediatrics 2014.
- Much of the following is adapted from that source, with updates based on changing technology for genetic testing in the intervening years.
- Reasons to pursue diagnostic genetic testing:
    - A definitive diagnosis (reduced uncertainty, access to support groups, reduction in invasive diagnostic testing)
    - Ability to provide a more detailed prognosis for the child
    - Potential for treatment or management specific to the diagnosis
    - Determination of recurrence risk for the parents and other family members
- History and physical examination
    - Is there a known family history of a specific genetic condition?
    - Does the history or physical exam implicate a specific genetic diagnosis based on physical features or characteristic history (e.g. Down Syndrome, Prader Willi)?
    - Is there an aspect of the history that makes a genetic diagnosis less likely (e.g. extreme prematurity, prenatal exposure to alcohol, history of traumatic brain injury, history of meningitis)?
        - A reference for non-genetic considerations for etiological diagnosis in patients with developmental delay can be found in the attached documents.
    - If targeted testing is indicated then can contact genetics for advice on the logistics of testing or refer at that time.
    - If no specific diagnosis is considered likely then consider the untargeted approach presented below.
- MRI of the brain
    - Not necessarily indicated in all patients with developmental delay
    - Higher yield for providing actionable information in the following settings:
        - Epilepsy
        - Macrocephaly
        - Microcephaly

        - Focal neurological findings (e.g. asymmetry, ataxia, hypertonia, dystonia, concern for elevated intracranial pressure, etc.)
        - Developmental regression
    - If MRI findings are specific (e.g. Leigh syndrome, cerebellar atrophy, cortical dysplasias, etc.) then consider targeted testing for that indication with advice from genetics or refer at that time.
    - If MRI is not obtained or if findings are normal or nonspecific then consider the untargeted approach presented below.

<u>Untargeted approach to genetic testing for developmental delay</u>

- Tier 1
    - Chromosomal microarray
        - Provides copy number of most clinically significant genes (eg deletion, duplication, triplication); can diagnose aneuploidy
        - Roughly two-week turnaround time
        - Insurance authorization should be obtained prior to sending (or use a lab that will complete insurance authorization for you).
        - Informed consent for the following should be discussed prior to testing:
            - Diagnostic yield for the indication of developmental delay is about 10%-30% depending on the setting
            - Test will reveal if parents are related to one another
            - Test may have clearly diagnostic, clearly normal or ambiguous results
            - Ambiguous results may require testing of parents or other family members for follow-up; in other cases ambiguity cannot be resolved
            - May have secondary findings that are clinically-significant but unrelated to the reason for testing (e.g. cancer predisposition)
    - Fragile X trinucleotide repeat expansion analysis
        - Caused by a trinucleotide repeat that cannot be detected by methods other than targeted testing
        - X-linked disorder, but symptomatic females are not uncommon and thus testing is indicated in both sexes
        - Insurance authorization and informed consent should be obtained prior to testing
        - Diagnostic yield is 1%-2% in boys, lower in girls
        - Informed consent:
            - With diagnostic results, mother may be a full mutation or premutation carrier, results may have implications for her fertility and potential for adult-onset neurological disease in premutation carriers
- Tier 2
    - Large gene sequencing panel of developmental delay-associated genes

        - Ideally trio-based including both biological parents to reduce the likelihood of uncertain variants; if not trio testing initially, then parental samples are likely to be needed subsequently for confirmation of diagnosis
        - Insurance authorization and informed consent should be obtained prior to testing (or use a lab that will complete insurance authorization for you).
        - Informed consent includes:
            - Any time child and parents are tested, there is the possibility to reveal that one of the parents is not the biological parent of the child
            - Diagnostic yield is probably about 30%, but depends on many factors
            - Ambiguous findings are common; some can be resolved with further testing, others cannot
            - Secondary findings are possible - detection of a diagnosis that does not account for the patient's entire presentation but still has clinical relevance
            - A parent could also receive the same diagnosis as the child as a result of testing
- Tier 3
    - Whole exome or whole genome sequencing can be considered.
    - See www.treatable-id.org for a testing algorithm and information on diagnoses that have specific management and can be detected with biochemical testing
    - Samples should ideally be obtained 3-4 hours after eating
    - Informed consent:
        - There are often abnormal but nonspecific findings in metabolic testing and further testing is often required as a result.
    - Algorithm includes:
        - Serum amino acids
        - Serum homocysteine
        - Urine creatine metabolites
        - Urine organic acids
        - Urine purines and pyrimidines
        - Urine oligosaccharides
        - Urine mucopolysaccharides

<u>Genetic testing laboratories that currently offer patient insurance benefit verification service:</u>

- Patient insurance benefit verification may be available at other labs as well and the availability of this service may change.
- Some laboratories have subsidies available to limit out of pocket cost to families.
- We recommend assessing the availability of these services with the specific lab that will be used at the time that testing is obtained.
- Most genetic tests can now be performed with buccal swab sample kits from the labs.

Return of results

- Labs will classify each reported genetic variant as either benign, likely benign, variant of uncertain significance (VUS), likely pathogenic or pathogenic.
- Likely pathogenic or pathogenic results can usually be reported as diagnostic to families if clinical features are compatible with that diagnosis.
- A VUS may require interpretation from a geneticist and additional testing of the child and family members.
- If there are questions about the significance of a result, then we recommend discussion with a geneticist prior to disclosing to the family.

Author

Austin Larson, MD
Assistant Professor, Pediatrics
University of Colorado School of Medicine
Children's Hospital Colorado

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Consent for Genetic Testing

Genetic testing may help determine an individual's diagnosis however it can be complex. In many cases, a genetic test directly detects an abnormality. There are different types of genetic testing. Molecular testing may detect a change in the DNA (variant). Cytogenetic testing may identify whether there is extra, missing, or rearranged genetic material. Most tests are highly sensitive and specific. However, sensitivity and specificity are test-dependent.

Providing accurate information about symptoms and family history enables correct test interpretation. Refer to test specific information for the general description of the test, purpose, and description of associated disorders.

Results from genetic testing may be positive, negative, or inconclusive.

- A positive result is an indication a person is affected with, a carrier of, or at risk for developing a certain disorder.
- A negative result does not exclude the possibility of being affected with or a carrier of a genetic disorder.
- An inconclusive result may occur due to limitations of laboratory methods, limitations in knowledge of the meaning of identified variant(s), or poor sample quality.

Identified genetic variants are interpreted using current information in medical literature and scientific databases. Since this information can change, a revised report may be issued if the meaning of the variant changes. Individuals with a variant of uncertain significance should contact their healthcare provider periodically to determine if new information is available.

Because of the complexity of genetic testing and the important implications of the test results, results will be reported only through a physician, genetic counselor, or other identified health care provider. The results are confidential to the extent allowed by law. They will only be released to other medical professionals or other parties with your written consent or as otherwise allowed by law.

Participation in genetic testing is completely voluntary. You can choose not to have genetic testing. In this case, you/your child may still benefit from a referral to a pediatric genetics clinic. Without genetic testing there is a possibility there is a treatable cause that is not identified without testing.

Signatures: My signature below acknowledges my voluntary participation in this test.

I hereby consent for my child _____ (print name)

to participate in genetic testing for _____

Patient/Parent/Guardian Signature	Date
Printed Name	
Witness Signature	Date
Printed Name	
Provider's Signature	Date
Printed Name	

Elements of Consent for Genetic Testing: Chromosomal Microarray Analysis (CMA)

The potential implications of genetic testing differ from other clinical tests and, therefore, require informed consent. The elements of the consent process are similar to other studies or procedures (describing the test, limitations, risks, and benefits to the patient). However, there are also specific disclosures that are important for the patient/parent to understand. The basic elements below are taken from the Texas Medical Association. (https://www.texmed.org/Template.aspx?id=1745)

Discussion

Informed consent begins with a discussion of the test. The following issues should be discussed when obtaining consent for Chromosomal Microarray Analysis (CMA) for evaluation of developmental delay. The provider may also choose to use educational materials that help to explain CMA and basic genetic principles to a patient/parent.

- Differential diagnosis
  - The child has exhibited signs of developmental delay, and the exact reason is unknown. One possible cause is a genetic abnormality (the provider may wish to refer to **Non-Genetic Causes of Developmental Delay** document).
- Description and purpose of the test
  - Chromosomal Microarray Analysis is a comprehensive technique by which chromosomes are analyzed for copy number variants, in other words, small deletions or duplications of genetic material. Abnormalities detected by CMA can reveal an underlying genetic cause for the child's developmental delay (the provider may wish to refer to **CMA** document).
- Benefits and expected outcome
  - Determining a diagnosis helps the family and their providers better understand the child's condition and can help to guide management and treatment decisions. Sometimes, results of a CMA help to identify the cause of the diagnosis and to predict whether it may affect other individuals in the family (the provider may wish to refer to the **CMA** document).
  - CMA results can be positive, meaning that one or more small deletions or duplications of genetic material were found that may explain the patient's developmental delay or other clinical symptoms. Alternatively, results can be negative, meaning that no deletions or duplications were found. However, it is still possible that the patient's delay may have a different genetic cause. There can also be chromosomal variations of uncertain significance. This means that a change in genetic material was identified but it is unclear whether it explains or causes any clinical symptoms.
- Risks associated with testing (see **CMA** document)
  - Sometimes, a CMA may show that a child has very similar copy number variants on the chromosomes they received from their father as they do on

the chromosomes they received from their mother. This result indicates that perhaps the child's parents are related by blood, for instance as cousins.
    - If a deletion or duplication is found in the child, testing of the parents is typically recommended as well. If one of the parents has the same deletion or duplication and yet does not have developmental delay or the same clinical symptoms as the child, it is less likely that the deletion or duplication caused the child's symptoms. By contrast, if the deletion or duplication occurred anew in the child, it is more likely to explain his/her clinical symptoms. It is important to note that, in doing parental testing, it is sometimes possible to identify misattributed paternity. In other words, the father who was tested is not the biological father of the child.
- Alternatives to testing
    - The patient/parent can choose not to have a CMA done. In this case, the child may still benefit from referrals for developmental therapies to try to address the symptoms of developmental delay.
    - To further evaluate for the underlying cause of the delay and to better understand the possible chance for other family members to be affected, the family may still benefit from referrals to Genetic or Developmental Pediatric specialists, even if they do not wish to pursue genetic testing.
    - Other biochemical tests, genetic tests and imaging studies may also be considered.
- Consequences of no testing
    - Without having a CMA or other tests done, the cause of the child's developmental delay may go unknown. In some cases, there may be a treatable cause that is not identified without testing. There may also be additional health problems for which the child may be at risk that are not identified without testing. Additionally, it may not be possible to determine whether other family members may be at risk for related symptoms.
    - Treatments and therapies aimed at the child's symptoms may be beneficial but also may not address the child's specific problem.

Education

- See available hand outs

Obtaining Written Consent

- Each lab has its own consent form for CMA testing. Your institution may also have a consent form that you need to complete.

Chart Documentation

- The informed consent process should be documented in the medical record.

Author

Grace S. Miller
Intern, Texas Health Institute

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Laws Pertaining to Genetic Information

GINA: Genetic Information Nondiscrimination Act

- GINA is a federal law passed in 2008 that protects against insurance and employment discrimination[1]
- If state laws are stronger, they are enforced before GINA. GINA steps in if states give limited protection[1]
- Article I: Health Insurance
    - Health insurance agencies cannot request, require, or use genetic information to determine eligibility for insurance, premium, continued amounts, or coverage terms.
    - Family history or genetic test (illustrating carrier status/ or potential for a disease) cannot be considered as pre-existing condition
    - Cannot use info to discriminate even if information is obtained accidentally
    - Applies to most insurers
        - Through employer
        - Private insurance
        - Medicare supplemental policies for individuals who have Medicare
    - DOES NOT APPLY (Have policies that provide discrimination protection similar to GINA)
        - Members of US military who use Tricare
        - Vets who receive care from VA
        - IHS
        - Federal employees who get care through federal employees Health Benefits plan
        - Medicaid and Medicare[2]
    - DOES NOT STOP INSURERS from basing decisions about eligibility, coverage or premiums on current symptoms or diagnosis of health condition
        - Can't discriminate based on potential for disease but genetic testing can be used for insurance purposes to confirm a diagnosis with manifestation of disease
            - EX: Genetic testing that illustrates a patient *will* have Huntington's Disease cannot be used by insurance companies to raise premiums, etc. However, once a patient begins to show symptoms of Huntington's disease and is diagnosed, insurance companies can use the genetic test to confirm diagnosis and use the information to adjust premiums, justify treatment, etc.
    - Cannot request, require, or use predictive results
    - Genetic information about diagnosed conditions cannot be used against family members for their insurance purposes
    - Insurers can ask for tests to make decisions about whether or not they will pay for a test (minimum amount of information)
        - They can use genetic test results to confirm diagnosis and pay for treatment
- Article II: Employment (Agencies with 15+ people)[1,3]

    - Illegal to discriminate because of genetic information
    - Cannot be used to make decisions about employment
    - Restricts employers and other entities from requesting, requiring or purchasing test results
    - Limits disclosure
    - Cannot be harassed because of test results
    - Usually illegal for a covered entity to get information except
        - Inadvertently
        - For a voluntary wellness program
        - As a requirement to obtain FMLA
        - The information is publicly available (as long as don't go searching for it)
        - Program that monitors biological effects of toxins in the workplace when required by law
        - For law enforcement purposes
    - Unlawful to disclose information

Texas Genetic Information Testing[4]

- Protection against discrimination by employers with 15 or more employees, agencies, unions, and public employers about individual genetic characteristics
- Any health plan cannot use genetic information or refusal of an applicant to submit to a genetic test to reject, renew, increase premiums for or otherwise adversely affect eligibility for or coverage under the plan
- Licensing authority may not deny, suspend, revoke, or refuse to renew an occupational license based on genetic information or refusal to submit to a test
- Penalty if information is improperly disclosed
- Must keep genetic testing confidential unless authorized or unless required to by court order or by law
- Individuals have right to know result of genetic information

Colorado Genetic Discrimination[5]

- Genetic information is the unique property of the individual to whom the info pertains
- Availability of information is limited
- Prevents denial of access to group disability insurance or long-term care
- Info confidential and privileged
- Research facilitates can use genetic information as long as information is de-identified
- Insurers can't require performance of or perform genetic test without consent

[1] "GINA Help," GINA Help, June 2010, GINAhelp.org

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State	Laws	Summary
Utah	US § 26-45-101 et seq US § 53A-1-1401 et seq US §§ 31A-1-301 31A-22-620 31A-22-162	• An employer cannot use genetic information to discriminate • Genetic information cannot be treated as a pre-existing condition in the absence of a diagnosis • Health insurance agencies may not use genetic information to discriminate • Collection, retention, and disclosure of genetic information is prohibited, with some exceptions (law enforcement, newborn screening, anonymous research). Genetic information must be destroyed upon request.

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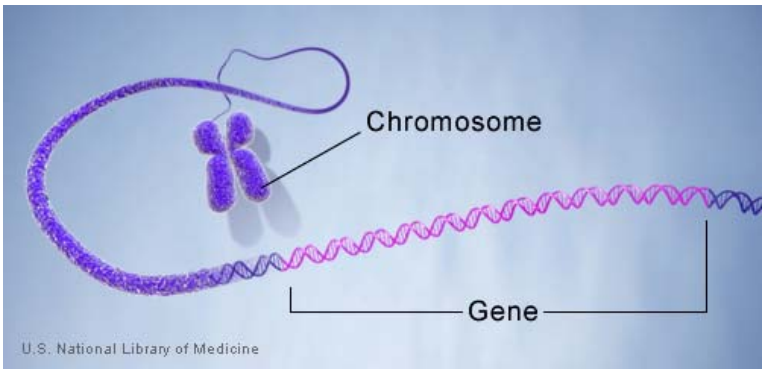
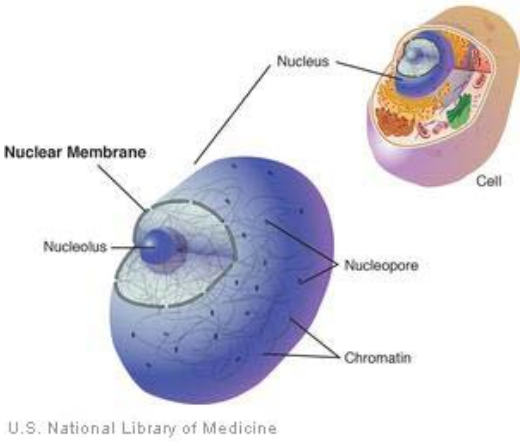
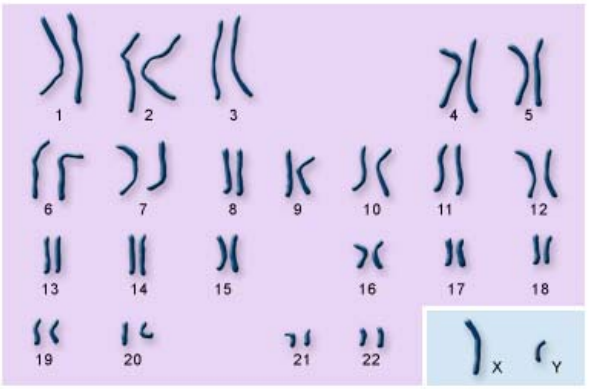
Genes: What They Are and What They Do



Each cell in the human body contains about 25,000 to 35,000 genes. They are found on tiny spaghetti-like structures called chromosomes, which are found inside cells. Your body is made of billions of cells, which are the very small units that make up all living things.

Most cells have one nucleus. The nucleus is a small egg-shaped structure inside the cell, and it has many parts. The nucleus acts like the brain of the cell. It tells every part of the cell what to do. It contains our chromosomes and genes. As tiny as it is, the nucleus has more information in it than the biggest dictionary you've ever seen.



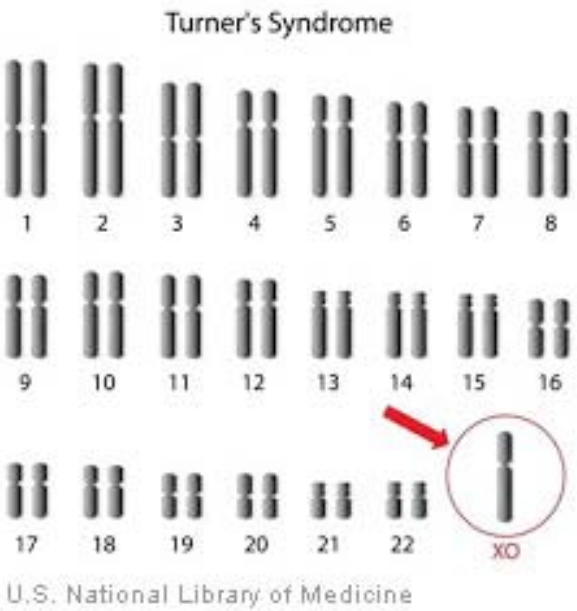


Chromosomes come in matching pairs and there are hundreds — sometimes thousands — of genes in just one chromosome. In humans, a cell nucleus contains 46 individual chromosomes or 23 pairs of chromosomes. Half of these chromosomes come from one parent and half come from the other parent.

Under the microscope, we can see that chromosomes come in different lengths and striping patterns. When they are lined up by size and similar striping pattern, the first twenty-two of the pairs are called autosomes; the final pair of chromosomes is called sex chromosomes, X and Y. The sex chromosomes determine whether you're a boy or a girl: females have two X chromosomes while males have one X and one Y.

Like chromosomes, genes also come in pairs. Each of your parents has two copies of each of their genes, and each parent passes along just one copy to make up the genes you have. Genes that are passed on to you determine many of your traits, such as your hair color and skin color.

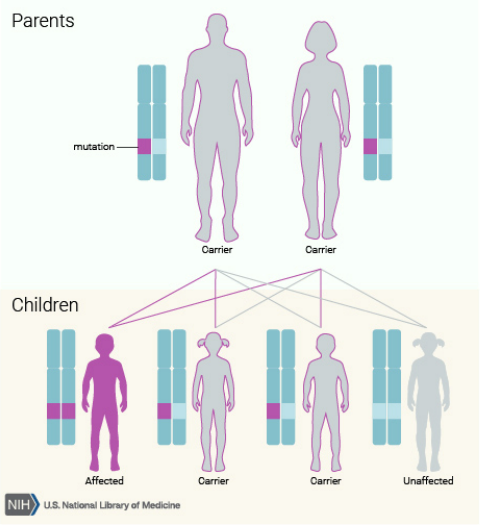
The chromosomes and genes contain DNA. This DNA spells out specific instructions—much like in a cookbook recipe — for making proteins in the cell. Proteins are the building blocks for everything in your body. Bones and teeth, hair and earlobes, muscles and blood, are all made up of proteins. Those proteins help our bodies grow, work properly, and stay healthy. Scientists today estimate that each gene in the body may make as many as 10 different proteins. That's more than 300,000 proteins!



Turner Syndrome is one type of genetic condition where a girl is born with only one X Chromosome. This can make the girl short and unable to have children later in life.

Doctors and scientists are studying genes to try to help people with hereditary problems. They want to know which proteins each gene makes and what those proteins do. They also want to know what illnesses are caused by genes that don't work right. Changes in genes are called mutations. Mutations may often be the cause of learning difficulties and many other health challenges. Other illnesses and health difficulties happen when there are missing genes or extra parts of genes or chromosomes.

Some of these gene problems can be inherited from a parent. For example, take the gene that helps the body make hemoglobin. Hemoglobin is an important protein needed for red blood cells to carry oxygen throughout the body. If parents pass on altered hemoglobin genes to their child, the child might only be able to make a type of hemoglobin that doesn't work properly. This can cause a condition known as anemia, a



Sickle cell anemia is one kind of anemia that is passed on through genes from parents to children.

condition in which a person has fewer healthy red blood cells.

Other gene problems do not come from parents but are new to the child. Copying genes over and over to make the many, many cells of the body often results in mistakes in the genes. Most of the time, the mistakes are caught and corrected by our body; sometimes they are not. This can result in a new problem in a child.

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Text modified from Narcisa, Vivien L. "What is a Gene?"KidsHealth from Nemours. March 2014. Accessed August 6, 2018. https://kidshealth.org/en/kids/what-is-gene.html

Images:

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Grace S. Miller
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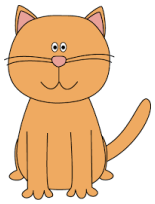
Variants of Uncertain Significance (VUS)

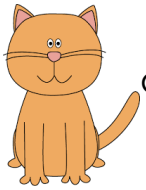
Sometimes, mutations or "spelling errors" occur in your DNA. This can sometimes change the meaning of the DNA which can affect your body.

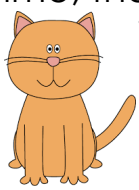
Let's use the spelling of  to help understand how these errors work.

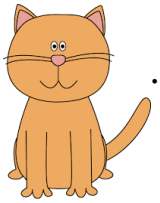
Normally, this animal's name is spelled C-A-T.

Sometimes, a person might misspell it K-A-T.
Although spelling it with a K is technically wrong, you can still tell that they are referring to a  .

In genetics, sometimes the strand of DNA is also "misspelled," but like this example, the meaning doesn't change. This is "benign," which means that the spelling error is not harmful and will not cause a genetic disorder.

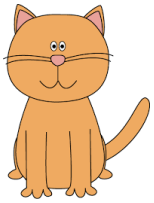
Other times, someone might misspell  as R-A-T.

This time, the meaning of the word has changed. Instead of referring to a  it refers to a  .

This can cause a problem if the person wants to refer to a  .

This can also happen with DNA, where the "spelling error" completely changes the meaning. This can be "pathogenic," which means that this spelling error can cause a genetic disorder.

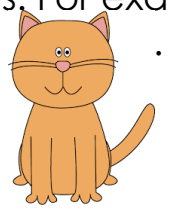
Other times, the spelling errors are not so understandable. If



is spelled C-R-T, C-E-T, or C-I-T, it is unclear what the person spelling the word is referring to.

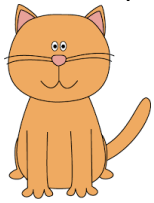
This can also happen in genetics. Sometimes geneticists don't know yet how a "spelling error" can affect the meaning of your DNA and therefore if it causes genetic disorders or not. These spelling errors are called "Variants of Uncertain Significance."

After some studies are done, scientists may know more about certain variants. For example, scientists may decide that C-E-T most likely means .



In DNA, this means that the variant is "likely benign," or likely to not cause disease.

Other variants might be reclassified as "likely pathogenic." For example, scientists may decide that C-I-T is not likely to refer to a



.

This means that the variant is likely to cause a genetic disorder.

What Does that Mean for My Diagnosis?

If you get a test result back that says you have a Variant of Uncertain Significance, that means that doctors don't know yet if your "spelling error" causes a specific genetic diagnosis. This doesn't mean you have a disease, but it also doesn't mean that you are fine. Doctors simply don't know. Doctors will use family history and symptoms to address your current medical concerns. In the future, doctors may know more about your variant.

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Author

Grace S. Miller
Intern, Texas Health Institute

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Variantes de Significado Incierto

Algunas veces, mutaciones o "errores de ortografía" ocurren en su ADN. Esto puede causar algunos cambios en el significado del ADN el cual puede afectar a su cuerpo.

Usemos la  palabra para ayudarnos a entender como estos errores funcionan.

Normalmente, el nombre de este animal se escribe G-A-T-O.

Algunas veces, algunas personas puede que lo escriban J-A-T-O. Aunque escribiéndolo con una J está técnicamente mal escrito, igual se puede entender que una persona se está refiriendo a un 

En genética, a veces las cadenas de ADN también pueden estar "mal escritas" pero como en este ejemplo, el significado no cambia. Esto es un cambio "benigno", que significa que el error no causa cambios o daños y no va a causar un desorden genético.

Otras veces, alguien puede  escribir como P-A-T-O.

Esta vez, el significado de la palabra ha cambiado. En vez de referirse a un 

se refiere a un  .

Esto puede causar un problema si la persona quiere referirse a un 

Esto también puede pasar en el ADN, donde la falta ortográfica completamente cambia el significado. Esto puede ser un cambio "patógeno", lo que significa que este error puede causar un desorden genético.

Otras veces, los errores no son tan fáciles de entender. Si  está escrito como G-E-T-R, G-I-T-O, o G-H-T-E, no está claro a que palabra la persona se está refiriendo.

Esto también puede ocurrir en genética. Algunas veces médicos de genética no saben todavía como esos errores ortográficos pueden afectar el significado del ADN y por eso no saben si causan desordenes o no. Estos errores se llaman Variantes de Significado Incierto.

Después de algunos estudios, los científicos saben más sobre algunas variantes. Por ejemplo, científicos pueden decidir que G-  I-T-O probablemente significa

En ADN, esto significa que la variante es "probablemente benigna" o la posible causa de una enfermedad.

Otras variantes pueden ser clasificadas como "posiblemente patogénicas". Por ejemplo, científicos pueden decidir que G-I-T-O no es necesariamente como la persona se refiere a 

Esto significa que la variante es la causa clave de un desorden genético.

¿Cuál es el significado para mi diagnostico?

Si usted recibe un resultado que dice que tiene una Variante de Significado Incierto, esto significa que los doctores no están seguros que sus "errores ortográficos" causan desordenes genéticos específicos. Esto no significa que usted tenga una enfermedad, pero tampoco significa que usted este sano. Los doctores simplemente no están seguros. Los doctores usaran sus antecedentes familiares y sus síntomas para discutir sus malestares médicos actuales. En el futuro, es posible que los doctores sepan más sobre su variante.

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Autor

Grace S. Miller

Intern, Texas Health Institute

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Why was my child referred to a medical genetic clinic?

(What is Medical Genetics?)

Why was my child referred to a medical genetic clinic?

Some children are born with differences in body structure, growth, brain development, or body chemistry that can lead to problems with health, development, school performance, and/or social interaction.

Your child has been referred to genetics clinic because you or your physician are concerned about why your child may have these medical problems or developmental (learning) problems.

What is medical Genetics?

- Medical genetics is a medical specialty, just like cardiology, or the ear, nose, and throat doctor.
- Medical geneticists and genetic counselors are the health care providers that work in medical genetics.
- Medical genetics deals with health problems that are caused or thought to be caused by changes in our genetic material
-

What is a gene?

Genes are the body's blueprints that determines the way our body works including our physical features, such as hair color, eye color but also how we are formed and developed. Genes can cause genetic conditions or disease that may be passed from parents to their children ("inherited").

There are thousands of documented genetic conditions, but the most common conditions include the following:

- Chromosomal changes (e.g. Down syndrome), which cause birth defects, intellectual/developmental disabilities and/or reproductive problems
- Single gene disorders such as cystic fibrosis, muscular dystrophy, Huntington's disease and sickle cell disease

- Birth defects such as spina bifida, cleft lip and cleft palate may have a genetic component

Why is it important to go to a genetics clinic if my child's medical problems are already being treated?

First, if your child is diagnosed with a specific genetic condition, medical providers may be able to give you more information about what can be done for your child including treatment or what can be expected in the future. Second, your child's condition may be inherited. It may have been passed down from family members who may or may not show signs of the medical condition. If your child's condition is inherited you can learn if this condition may also affect you, other family members or possible future pregnancies in your family.

Who can refer my child to the genetic clinic?

A doctor, physician assistant or nurse practitioner can refer your child to a genetics clinic. Sometimes parents can also call the genetics clinics directly to schedule an appointment.

How long will I have to wait for an appointment?

As there are few genetic service providers in most areas, you may have to wait from 3 to 6 months for an appointment at the genetics clinic.

What happens at a medical genetics clinic visit and after?

Who will my child see at a genetic clinic?

Genetic services are often provided through a team of medical providers**.**

- A medical doctor, a physician assistant or a nurse practitioner who specializes in medical genetics
- A genetic counselor
- Other medical professionals such as nurses, medical students or resident doctors.

What should I expect at my child's appointment?

Most genetic clinic appointments last 45 to 60 minutes. You may want to bring someone with you that can help you ask questions and take notes. At a genetics clinic you can expect the following:

- You will discuss your child's health and developmental concerns with the genetic provider.
- The genetic counselor will collect your child's family health history:
    - You will be asked about the health/developmental history of your child's siblings, parents, aunts, uncles, cousins, and grandparents. This information helps the genetics

team figure out if your child's condition may be related to other health issues in the family.
    - Please bring as much information about the health of family members as possible.
- A physical examination of your child and possibly other family members will be performed by the medical geneticist.
- The medical geneticist may take photographs to document certain physical features of your child.
- The medical geneticist will explain any findings to you and discuss options for further evaluation if needed.
- You will be encouraged to ask questions, and you, the geneticist and the genetic counselor will decide together about any further testing and evaluations.

What kind of tests are done in a genetic clinic?

- Tests on blood and/or urine samples may be ordered for your child. These samples may be collected on the day of the clinic visit. Others testing such as x-rays or MRIs may be ordered but generally cannot be done on the day of the clinic visit.
- Some genetic testing may require authorization from your insurance company due to cost, before it can be started. The insurance authorization process can take up to three months. If the insurance company approves the test and a sample is obtained and sent, it may take 4 to 6 weeks to receive results. Sometimes insurance companies may not approve genetic testing, and the testing may not be performed unless you can pay for the test yourself which can be thousands of dollars.

Will my child be diagnosed at the first genetic clinic visits?

Probably not. It can often take a while, maybe many months, before a child is diagnosed. Sometimes a child may not be diagnosed.

What happens next if my child is diagnosed with a genetic condition?

A genetic counseling appointment may be offered to discuss your child's condition, how this condition may be inherited and whether other family members may benefit from testing. A letter will be written to the referring health professional about your child's genetic condition and a copy may be sent to you. Your child may or may not need to return to genetics clinic or be referred to other medical specialists. Many times, the referring medical provider can provide care for the condition with guidance from the genetics team.

What happens next if my child is not diagnosed with a genetic condition?

The referring health professional will receive a letter from the genetics team summarizing your visit and the findings. The referring health provider will continue with your child's care. However, your child may still return to the genetics clinic once every one or two years in case new testing becomes available for your child.

Descripción de los servicios genéticos para familias
20 de octubre 2018

¿Por qué remitieron a mi hijo(a) a una clínica de medicina genética?

¿Por qué remitieron a mi hijo(a) a una clínica de medicina genética?

Algunos niños nacen con diferencias en la estructura corporal, el crecimiento, el desarrollo cerebral o la química corporal. Estas diferencias pueden provocar problemas de salud, desarrollo, rendimiento escolar o interacción social.

Otros niños pueden tener un resultado positivo de una prueba de detección que se realiza a todos los recién nacidos. Esta prueba de detección de los recién nacidos es a través de un examen de sangre y permiten que los profesionales médicos identifiquen y traten ciertas condiciones graves antes de que el bebé se enferme.

A su hijo(a) lo/la han referido a una clínica de genética porque a usted o a su médico les preocupa el motivo por el cual su hijo(a) tiene estos problemas de salud o de desarrollo (aprendizaje) o ha obtenido un resultado positivo en la prueba de detección para recién nacidos.

¿Qué es la medicina genética?

- La medicina genética es una especialidad médica, al igual que cardiología o neurología.
- Los médicos genetistas y los consejeros de genética son los proveedores de atención médica que trabajan en la clínica de medicina genética.
- La medicina genética estudia problemas de salud causados o presuntamente causados por cambios en nuestro material genético.

¿Qué es un gen?

Los genes llevan información en cada uno de nosotros y desempeñan un papel muy importante en la determinación de cómo funciona nuestro cuerpo, lo cual afecta nuestros rasgos físicos, por ejemplo el color del cabello o de los ojos, pero también cómo nos formamos y desarrollamos. Los genes también pueden causar condiciones o enfermedades genéticas que pueden transmitirse de padres a hijos ("condiciones hereditarias").

Se han registrado miles de condiciones genéticas, pero algunas de las más comunes son las siguientes:

- Cambios cromosómicos (por ejemplo, síndrome de Down), que causan defectos de nacimiento, discapacidades intelectuales/del desarrollo o problemas reproductivos.
- Trastornos de un solo gen como la fibrosis quística, la distrofia muscular, la enfermedad de Huntington, la fenilcetonuria y la anemia drepanocítica.
- Los defectos congénitos como la espina bífida, el labio leporino y el paladar hendido pueden tener un componente genético.

¿Por qué es importante ir a una clínica de genética si los problemas de salud de mi hijo(a) ya se están tratando?

Primero, si a su hijo(a) le diagnostican una condición genética, es posible que los proveedores médicos le puedan brindar más información sobre lo que se puede hacer por él/ella, por ejemplo, un tratamiento, o sobre las expectativas de salud para el futuro. Segundo, la afección de su hijo(a) puede ser hereditaria. Puede haber sido transmitida por miembros de la familia que tal vez tengan síntomas de la afección o no. Si la condición de su hijo(a) es hereditaria, la clínica de genética puede averiguar si también puede afectarlo(a) a usted, a otros miembros de la familia o a embarazos futuros de su familia.

¿Quién puede referir a mi hijo(a) a la clínica de genética?

Un médico, un asistente médico o un profesional de enfermería pueden referir a su hijo(a) a una clínica de genética. A veces, los padres también pueden llamar a las clínicas de genética directamente para pedir una cita.

¿Cuánto tiempo tendré que esperar para una cita?

Como hay pocos proveedores de servicios genéticos en la mayoría de las áreas, es posible que tenga que esperar de 3 a 6 meses para conseguir una cita en la clínica de genética.

¿Qué sucede en una consulta en la clínica de medicina genética? ¿Y después?

¿A quién verá mi hijo(a) en la clínica de genética?

Por lo general, un equipo de proveedores médicos brinda los servicios genéticos.

- Un médico, un asistente médico o un profesional de enfermería especializados en medicina genética.
- Un consejero genético.
- Otros profesionales médicos como enfermeros, estudiantes de medicina o médicos residentes.

¿Qué debo tener en cuenta para la cita de mi hijo(a)?

La mayoría de las citas en las clínicas de genética duran de 45 a 60 minutos. Es posible que desee llevar a un familiar o amigo(a) que pueda ayudarlo(a) a hacer preguntas y tomar notas. En una clínica de genética debe tener en cuenta lo siguiente:

- Usted hablará de sus preocupaciones sobre la salud y el desarrollo de hijo(a) con el médico genetista.
- El consejero genético recopilará el historial de salud de los familiares de su hijo(a):
    - Le preguntarán acerca del historial de salud y desarrollo de los hermanos, los padres, los tíos, los primos y los abuelos de su hijo(a). Esta información ayuda al equipo de genética a determinar si la afección de su hijo(a) puede estar relacionada con otros problemas de salud de la familia.
    - Lleve a la cita toda la información que tenga sobre el historial de salud de los miembros de la familia.
- El médico genetista realizará un examen físico de su hijo(a) y posiblemente de otros miembros de la familia.
- El médico genetista puede tomar fotografías para registrar ciertas características físicas de su hijo(a).
- El médico genetista le explicará cualquier resultado obtenido y hablará con usted sobre las opciones de evaluación adicionales si es necesario.
- Le sugerirán que haga preguntas, y usted, el genetista y el consejero genético decidirán juntos si se realizarán otras pruebas y evaluaciones.

¿Qué tipo de pruebas se realizan en una clínica de genética?

- Se pueden solicitar análisis de muestras de sangre u orina de su hijo(a). Esas muestras se pueden recolectar el día de la consulta en la clínica. Otras pruebas pueden ser ordenadas como radiografías o resonancias magnéticas, pero generalmente no se hacen el día de la consulta en la clínica.

- Debido al costo, antes de realizar algunas pruebas genéticas, es posible que se requiera la autorización de su compañía aseguradora o de Medicaid. El proceso de autorización del seguro puede tomar hasta tres meses. Una vez autorizada, la prueba se recolecta y se envía una muestra. Los resultados pueden tardar de 4 a 6 semanas. A veces, las compañías aseguradoras no autorizan las pruebas genéticas, y estas no se realizan a menos que usted mismo pueda pagarlas, lo cual puede costar miles de dólares.

¿Recibirá mi hijo(a) un diagnóstico en la primera consulta en la clínica de genética?

Probablemente no. Por lo general el diagnóstico puede tomar un tiempo, tal vez muchos meses. Algunas veces no se encuentra el diagnóstico.

¿Qué pasa si a mi hijo(a) le diagnostican una condición genética?

Se puede ofrecer una cita con un consejero de genética para hablar sobre la condición de su hijo(a), cómo esa condición puede ser hereditaria y si otros miembros de la familia podrían obtener algún beneficio con las pruebas. Se escribirá una carta al proveedor médico remitente acerca de la condición genética de su hijo(a) y usted podrá recibir una copia. Es posible que su hijo(a) deba regresar a la clínica de genética o que deban remitirlo(a) a otros especialistas médicos. Muchas veces, el proveedor médico remitente puede brindar un tratamiento para la condición de su hijo(a) con la orientación del equipo de genética.

¿Qué sucede si a mi hijo(a) no le diagnostican ninguna afección genética?

El proveedor médico que remitió a su hijo(a) recibirá una carta del equipo de genética en la que se resuma su consulta y los resultados. El proveedor médico remitente continuará brindándole atención médica a su hijo(a). Sin embargo, su hijo(a) podría regresar a la clínica de genética una vez cada uno o dos años si es que surgen nuevas pruebas.

July 11, 2018

OVERVIEW OF UTAH TEAM PROJECT

YEAR 1

1. Project Name

Early Genetic Intervention for Children with Developmental Delays

2. Project Background

The population of children with developmental delays in Utah is large and the wait time for these children to receive genetic testing is long. Additionally, many of these children are never referred for genetic testing. We have found that many pediatricians are not aware of the increasing number of disorders being found to be the cause of developmental delays, including Autism, and the benefits and decreasing costs of such testing.

This project aims to:

1. Educate pediatricians in Utah on the benefits and low costs of ordering genetic testing prior to a referral to genetics.
2. Provide an algorithm for identifying patients that should be offered testing.
3. Provide a list of laboratories that offer robust panels and help with insurance authorization.
4. Provide a support network to pediatricians that order testing and have questions regarding the results they receive.

3. Project Summary

1. The team will first develop the educational materials needed to share with Utah pediatricians.
2. Materials will be delivered to a pilot group of pediatricians and feedback will be recorded.
3. Educational materials will be updated as necessary and a distribution strategy will be planned.
4. Educational materials will be distributed at the state level.
5. Feedback and adjustments will be ongoing.
6. Data will be collected for progress reports to MSRGN.

4. Population/Community the Project Intends to Serve

This project will serve the undiagnosed Developmentally Delayed population.

5. Project Timeframe

May 2018 – May 2020

6. Expected Outcomes

We expect to see a significant increase in genetic testing at the primary care physician level, leading to a larger percentage of children with developmental delays with a diagnosis. We also expect to see an increase in communication between genetics and pediatricians.

7. Data Collection Plans for Measurable Change

In the final year of the project we will also select a diverse group of pediatricians to survey for participation and extrapolate those results to estimate the increase in testing.

8. Project Leads

Heidi Wallis 801-712-8826 | heidiwallis@utah.gov

Chuck Norlin 801-581-2205 | Chuck.Norlin@hsc.utah.edu