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Illumina Laboratory Services
CLIA No.: 05D1092911
CAP No.: 7217613

Illumina Laboratory Services

TruGenome™ Undiagnosed Disease Test Requisition Form

The TruGenome Undiagnosed Disease Test is intended to provide information to physicians to aid in the diagnosis of rare and undiagnosed genetic diseases. The analysis and interpretation are designed to detect and report on single nucleotide variants (SNVs), small insertion/deletion events, copy number variants (CNVs), homozygous loss of SMN1, mitochondrial SNVs and a set of short tandem repeat (STR) expansions associated with genetic conditions. Proband-only and/or family-based analysis is performed, depending on the availability of samples at the time of testing. A family-based analysis may be comprised of a trio (the proband and their biological parents), a duo (parent and child) or other family structures. Variant characteristics, clinical presentation information, plausible inheritance patterns (based on the reported family history), peer-reviewed literature and information from publicly available datasets are used to contextualize variants identified during analysis.

This test is appropriate in cases where there is a suspicion of a genetic condition with clinical and genetic heterogeneity and numerous candidate genes to be assessed. The evaluation of the genome may clarify or refine a diagnosis because the presenting set of symptoms, imaging and laboratory tests (biochemical and molecular) are inconclusive, or in cases where the phenotype might indicate multiple genetic conditions.

This test is not appropriate for certain conditions, including those caused by multiple genes, each with a small effect, gene–environment interactions and methylation disorders. To assess if a patient's disorder is likely to have a Mendelian etiology, the referring physician should consider other lines of evidence such as increased severity, earlier than expected age of onset, multiple affected close family members and unexpected phenotypic complexity.

Physicians ordering this test should understand its intended use and performance characteristics. Physicians should provide pre-test counseling to their patients and the family members being tested to review the potential benefits, risks, limitations and alternatives to testing. Physicians ordering this test are responsible for obtaining informed consent from the persons being tested. Certain variants detected by the TruGenome Undiagnosed Disease Test may require orthogonal confirmation. In these cases, a portion of extracted DNA may be sent to an external laboratory for additional testing. Details are available upon request. Please review the test description at www.illumina.com/clinical/illumina_clinical_laboratory/trugenome-clinical-sequencing-services.html

Statement Regarding the TruGenome Undiagnosed Disease Test

- The TruGenome Undiagnosed Disease Test was developed, and its performance characteristics determined, by Illumina Laboratory Services. This test has not been cleared or approved by the US Food and Drug Administration (FDA). The laboratory is regulated under Clinical Laboratory Improvement Amendment (CLIA) as qualified to perform high-complexity testing. This test is intended for clinical purposes and should not be regarded as investigational or for research.
- The TruGenome Undiagnosed Disease Test will be performed at Illumina Laboratory Services. The laboratory is CLIA-certified and College of American Pathologists (CAP)-accredited.
- Illumina cannot accept samples from New York State.

To submit a sample for testing, please provide:

Test Requisition Form (TRF)

- Completed and signed test requisition form. Each person who submits a sample for testing at Illumina Laboratory Services is considered a patient. For family-based analysis, complete a new TRF for each family member.
- Clinical phenotype (TRF, section 4). Only *required* for affected proband and affected family members. Section 4 may be supplemented with copies of clinical notes.
- Project Identifier *(if applicable)*, or billing information *(if applicable)*.

Patient Sample

- For information about ordering clinical whole genome sequencing or obtaining whole blood collection kits: https://www.illumina.com/clinical/illumina_clinical_laboratory/how-to-order.html

Send the **completed** items listed above to:

Illumina, Inc.
ATTN: ILS - Illumina Laboratory Services
5200 Illumina Way, Building 2, Dock 2, San Diego, CA 92122

For questions, please contact Illumina Laboratory Services at (858) 736-8080, or (855) 266-6563 (toll free), or submit a secure ticket at clinicallabservicessupport.illumina.com

TruGenome Undiagnosed Disease Test Requisition

Place Barcode Here

For Laboratory Use Only	☐ Blood
Received	☐ DNA

Enter Project Identifier:

1. Requested Test
All fields below are required to be completed.

☐ TruGenome Undiagnosed Disease Test (Patient only)
☐ TruGenome Undiagnosed Disease Test (Family-based analysis)

- ***For family-based analysis, submit a test requisition form for each patient submitted for testing.***

2. Patient Information
Each person from whom a sample is taken and submitted for testing at Illumina Laboratory Services is considered a patient. For family-based analysis, complete a separate TRF for each family member.

First	Middle Initial	Last

Date of Birth (DD/MON/YYYY eg, 28/Feb/2017) **PLEASE WRITE THE MONTH eg, 28 FEB 2017** DAY/MONTH/YEAR	Biological Sex ☐ Male ☐ Female ☐ Unknown

Ethnicity (Optional) ☐ African ☐ Ashkenazi Jewish ☐ Latino ☐ East Asian ☐ European/Caucasian ☐ Middle Eastern ☐ Asian Pacific Islander ☐ Other _____

For the person being tested with respect to this test requisition form, select the appropriate relationship to the proband below.

Name of proband: _____

Number of family members being submitted for testing:

Relationship to Proband. Select one row only for the patient named on this requisition form.	Affected Status: Affected	Unaffected	Unknown
☐ Proband (affected individual in the family who is the primary individual being tested)	☐	☐	☐
☐ Biological mother of the proband	☐	☐	☐
☐ Biological father of the proband	☐	☐	☐
☐ Full brother of the proband	☐	☐	☐
☐ Full sister of the proband	☐	☐	☐
☐ Other [describe relationship to the proband specifically (eg, maternal half-sister of the proband)]	☐	☐	☐

For family members (mother, father, sibling, other) listed as affected above, please indicate if their clinical features are suspected to be due to the same etiology as the proband.

Yes ☐ No ☐

If no, please describe _____

3. Physician and Institution Information

Authorized Physician (Print Full Name)	NPI (or License if no NPI) Number
Institution Name	Institution Address (Required for Return of Results)
Physician Office Phone Number	

Physician Email (Required: Notification of return of results and to access clinical deliverables will be sent to this email address)

Names and email addresses of other health care providers who may receive delivery notification/copy of results

First	Last	Email Address
First	Last	Email Address

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4. Patient Clinical Information The clinical information on this form will be used in the clinical interpretation of the data. Failure to provide clinical information about the patient will result in delay of testing. In addition to completing the phenotype information, submit copies of relevant clinical notes and family history, if necessary.

Reason for referral for testing:

Main clinical features and phenotypes present in the patient under the appropriate category:
Abnormality of:

☐ Head or neck:	
☐ Eye:	
☐ Ear:	
☐ Voice:	
☐ Thoracic cavity:	
☐ Cardiovascular system:	
☐ Breast:	
☐ Respiratory system:	
☐ Limbs:	
☐ Musculature:	
☐ Skeletal system:	
☐ Connective tissue:	
☐ Digestive system:	
☐ Nervous system:	
☐ Genitourinary system:	
☐ Immune system:	
☐ Endocrine system:	
☐ Blood and blood-forming tissues:	
☐ Metabolism/homeostasis:	
☐ Integument:	
☐ Growth abnormality:	
☐ Prenatal development or birth:	
☐ Neoplasm:	
☐ Other:	

5. Secondary and Incidental Findings Analysis

Select one of the two options below (required):

A secondary findings analysis is available for each individual being tested as part of the TruGenome Undiagnosed Disease Test. This analysis includes a targeted screen of variants that meet the current test definition in genes recommended for reporting of secondary findings by the American College of Medical Genetics and Genomics (ACMG) SF v3.1 list of genes. The list of genes included in this analysis are:

ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CASQ2, COL3A1, DES, DSC2, DSG2, DSP, ENG, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1

☐ **Patient OPTS IN for secondary findings analysis**

☐ **Patient OPTS OUT of secondary findings analysis**

Important points to consider:

- Opting out of secondary findings analysis means that a targeted search for variants in the list of genes recommended by the ACMG for reporting of secondary findings will not be performed.
- Incidental findings (variants classified as pathogenic or likely pathogenic in genes that are unrelated to the patient's primary indication for testing and deemed reportable by the clinical laboratory director) will still be returned, if identified.
- If an individual opts out of the analysis, incidental findings related to ACMG guidelines may still be reported if the finding lies within a large reportable CNV that contains multiple genes, including those on the ACMG list.
- In the case of a family-based analysis (eg, the TruGenome Undiagnosed Disease Trio Test), identification of secondary findings in family members who opt in for the analysis may inform carrier status of other members of the family, even those who choose to opt out of the analysis.

Incidental findings (It is not possible to opt out of incidental findings.)

Incidental findings are defined as clinically significant variants found in genes associated with phenotypes that are unrelated to the patient's primary indication for testing. Unlike Secondary Findings, these variants are not actively sought, but may be noted during analysis. Variants with the potential to influence medical management, that meet the following criteria, and are deemed reportable by the clinical laboratory director will be returned.

- The evidence supporting the gene-disease relationship must be classified "Strong" or "Definitive" per current laboratory protocol.
- The variant(s) must reach a classification of likely pathogenic or pathogenic and occur in the correct allelic state (or zygosity) for the disease.
- Must influence medical management per the discretion of the laboratory director.
- Short tandem repeat (STR) expansions are not returned as incidental findings.

6. Pharmacogenomics Analysis

Select one of the two options below (required):

A pharmacogenomics analysis is available for each individual being tested as part of the TruGenome Undiagnosed Disease Test. This analysis includes detection and reporting of the clinical impact of well-established drug-gene associations (based on evidence and guidance from the Clinical Pharmacogenetics Implementation Consortium [CPIC], the US Food and Drug Administration [FDA], the Association for Molecular Pathology [AMP], and the American College of Medical Genetics and Genomics [ACMG]). The following genes are included in this analysis:

CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP4F2, CYP3A5, DPYD, SLCO1B1, TPMT, HLA-B (*57:01 proxy: *HCP5* rs2395029)

☐ **Patient OPTS IN for pharmacogenomics analysis**

☐ **Patient OPTS OUT of pharmacogenomics analysis**

Important points to consider:

- Opting out of pharmacogenomics analysis means that a targeted search for specific variants in the list of genes above will not be performed.
- In the case of a family-based analysis (eg, the TruGenome Undiagnosed Disease Trio Test), identification of pharmacogenomics findings in family members who opt in for the analysis may inform carrier status of other members of the family, even those who choose to opt out of the analysis.

7. Patient Sample Collection Information

Date of Collection	Sample Type
(DD/MON/YYYY eg, 28/Feb/2017) **PLEASE WRITE THE MONTH eg, 28 FEB 2017** DAY/MONTH/YEAR	☐ Blood ☐ DNA *Extracted DNA has a higher known failure rate than whole blood. Please contact the laboratory for more information. DNA must be collected from an authorized CLIA laboratory.*

8. Physician Signature

Please review the Illumina Patient Informed Consent Form with your patient prior to ordering this test.

I certify that: (i) the patient (or authorized representative on the patient's behalf) has given their informed consent (which includes written informed consent or written authorization when required by law) to have this genetic test performed, (ii) the informed consent obtained from the patient meets the requirements of applicable law and is materially similar to the attached Patient Informed Consent form, (iii) documentation of consent is maintained in the patient file and will be provided to Illumina upon request, (iv) I will notify Illumina if any patient withdraws or changes their consent, and (v) I am a licensed medical practitioner with the proper licensing in my state or country to order this testing. I agree to provide Illumina, or its designee, any and all information reasonably required for this genetic testing to be performed.

DAY/MONTH/YEAR

_____ _____

Authorized Physician Signature (required) | **Date (DD/MON/YYYY eg, 28/Feb/2017)**
PLEASE WRITE THE MONTH eg, 28 FEB 2017

9. Billing Information/Payment

- **NOTE: If you are part of a participating project or existing contract, payment information is not required.**
- The Responsible Party identified below agrees to pay the full price of the test. Illumina will not begin processing the sample until payment arrangements have been made. Testing will be delayed if payment arrangements have not been made.
- Illumina does not bill health insurers or institutional billing departments. If reimbursement is necessary or desired, the Responsible Party will make his/her own arrangement to receive reimbursement.

Select the most appropriate billing option (this is the Responsible Party)

☐ Facility/Contract Billing ☐ Facility/Physician billing must be prearranged	☐ Patient/Legal Guardian/Other
Facility Name	Name (Name of Responsible Party)
Address	Billing Address
City / State / Zip	City / State / Zip
Purchase Order No. / Contact Person	Phone / Email
Phone / Email	

I agree that I am financially responsible for the full amount of the test price.

_____ _____

Responsible Party Acknowledgement and Signature | **Date (DD/MON/YYYY eg, 28/Feb/2017)**

Select your payment option Bill my credit card for 100% prepayment Illumina can only accept credit cards from the US and Canada.	Cardholder Name Card Number	
Card Type ☐ Visa ☐ Mastercard ☐ American Express	Exp Date (MM/YYYY eg, 28/Feb/2017)	CVV