Hypophosphatemia is a below-normal concentration of serum phosphate that, when chronic, can have serious consequences for bones, muscles, and teeth. Certain hypophosphatemia disorders have an underlying genetic cause.

Hypophosphatemia disorders vary not only in their etiologies, but also in their symptoms and symptom severity. An accurate diagnosis of genetic hypophosphatemia disorders may have an impact on clinical management of the condition, including: customizing care to a patient’s specific needs, providing patients with the appropriate genetic counseling support, and connecting patients and their families to patient advocacy organizations and other resources.

This program provides testing for 17 different hypophosphatemia conditions, including X-linked hypophosphatemia (XLH), the most common form of genetic hypophosphatemia.

- X-linked hypophosphatemia
- Autosomal dominant hypophosphatemic rickets (ADHR)
- Autosomal recessive cystinosis
- Autosomal recessive hypophosphatemic rickets (ARHR) type 1
- Autosomal recessive hypophosphatemic rickets (ARHR) type 2
- Autosomal recessive hypophosphatemic rickets (ARHR) type 3 (Raine syndrome)
- Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)

- Hypophosphatasia (HPP)
- Infantile hypercalcemia
- McCune-Albright syndrome
- Osteoglophonic dysplasia (OGD)
- Tyrosinemia type 1
- Vitamin D–dependent rickets type 2A (VDDR2A)
- Vitamin D–dependent rickets type 1B (VDDR1B)
- Vitamin D–dependent rickets type 1A (VDDR1A)
- X-linked recessive hereditary hypophosphatemic rickets (Dent disease type 1)
- X-linked recessive Lowe syndrome

*Please note that clinical sensitivity for McCune-Albright syndrome, which is due to postzygotic somatic variants, is expected to be significantly reduced when analyzing non-lesional sample types (PMID: 25719192).
ENROLL YOUR PATIENTS IN SPONSORED GENETIC TESTING

ELIGIBILITY CRITERIA
In order to take part in no-charge, sponsored genetic testing for hypophosphatemia, patients must be aged **6 months and older AND:**

- have a previous diagnosis related to hypophosphatemia
- **OR** have a family member with a confirmed XLH diagnosis
- **OR** exhibit 2 or more of the following clinical signs and/or symptoms:
  - Family member of a patient with confirmed XLH
  - Short stature
  - Lower limb abnormalities
  - Fractures/pseudofractures
  - Tooth abscesses or excessive dental caries
  - Bone, joint pain, or joint stiffness
  - Muscle pain, weakness, or fatigue
  - Gait abnormalities
- **OR** have a completed UltraCare® Start Form for XLH

HOW TO SUBMIT A PATIENT TEST

- Obtain a blood, saliva, or buccal swab sample from your patient, using the provided sample collection kit. Mail the sample using the prepared packaging and prepaid label.

- Submit the Invitae Test Requisition Form:
  - Complete and print all pages of the fillable form. Mail the form with the patient sample, using the prepared packaging and prepaid label.

  For off-site sample collection:
  - **EITHER** complete and print all pages of the fillable form. Fax the form to **1-415-276-4164**.
  - **OR** complete the form online at invitae.com/hypophosphatemia.

  It is strongly encouraged to provide medical history, including clinical and biochemical findings, and family history information with the form and patient sample, when available. This information is useful for variant interpretation. Test results are usually available within 10 to 21 calendar days from when sample processing begins. You will be notified via email (or fax, if we do not have your email address) to access results through Invitae’s secure site.

FOR PATIENTS MEETING THE ELIGIBILITY CRITERIA, THIS PROGRAM IS PROVIDED AT NO CHARGE.

QUESTIONS ABOUT THE HYPOPHOSPHATEMIA TESTING PROGRAM?
To learn more about the hypophosphatemia testing program, contact an Ultragenyx team member or visit Invitae online at invitae.com/hypophosphatemia.

SCROLL DOWN FOR MORE INFORMATION ABOUT XLH AND HOW IT CAN AFFECT PATIENTS.
XLH IS THE MOST COMMON FORM OF GENETIC HYPOPHOSPHATEMIA\textsuperscript{3}

WHAT IS X-LINKED HYPOPHOSPHATEMIA?
XLH is a hereditary, progressive, chronic form of hypophosphatemia. It is caused by X-linked dominant genetic variants in the \textit{PHEX} gene that raise serum levels of fibroblast growth factor 23 (FGF23) through an unknown mechanism.\textsuperscript{2,4} The increase in FGF23 activity leads to lifelong renal phosphate wasting.\textsuperscript{4} Patients with XLH typically experience poor skeletal, muscular, and dental health and impaired physical function.\textsuperscript{2,4} XLH was previously known by many different names.

THE GENETIC MUTATION THAT CAUSES XLH IS INHERITED IN AN X-LINKED DOMINANT PATTERN.\textsuperscript{2}
The majority of patients with XLH inherit \textit{PHEX} mutations from an affected parent. However, approximately 20\% to 30\% of cases of XLH arise from spontaneous mutations in the \textit{PHEX} gene.\textsuperscript{7} XLH occurs in 1 in 20,000 to 1 in 25,000 live births.\textsuperscript{2}

OTHER NAMES FOR XLH\textsuperscript{1-3,5,6}
- X-linked hypophosphatemic rickets
- Hereditary hypophosphatemic rickets
- Familial hypophosphatemic rickets
- Vitamin D–resistant rickets (VDRR)
- Vitamin D–resistant osteomalacia
- X-linked vitamin D–resistant rickets
- Hypophosphatemic rickets
- Hypophosphatemic vitamin D–resistant rickets (HPDR)
- X-linked rickets (XLR)
- Genetic rickets
- Familial hypophosphatemia

SPONSORED GENETIC COUNSELING FOR ELIGIBLE PATIENTS
Ultagenyx has partnered with InformedDNA, a genetic counseling company, to provide genetic counseling at no charge to eligible patients and their family members or caregivers. These patients and caregivers are invited to contact InformedDNA at 1-888-744-8952 or visit InformedDNA.com/Ultagenyx to schedule an appointment with a board-certified genetic counselor.
Skeletal defects
• Rickets and osteomalacia, leading to short stature and bowing of the legs\(^2,4,8\)
• Bone and joint pain that accompanies rickets and osteomalacia\(^2,9\)
• Cranial defects such as Chiari malformations and craniosynostosis\(^2,8\)

Muscular dysfunction
• Muscular dysfunction such as muscle pain, stiffness, and weakness\(^1,8,9\)
• Muscle weakness, which can result in gait disturbances\(^1,8\)

Dental abnormalities
• Dental abscesses\(^4,8\)
• Tooth loss\(^8\)

Skeletal defects
• Bone and joint pain and fatigue, which can manifest due to osteomalacia\(^2,8,10\)
• Pseudofractures and fractures\(^2,4,8\)
• Short stature and lower extremity abnormalities\(^2,8\)
• Enthesopathy or calcification of the tendons\(^2,4,8\)
• Osteoarthritis\(^1,8\)

Muscular dysfunction
• Compounding muscular dysfunction, such as muscle pain, stiffness, weakness, and gait disturbances\(^1,8\)

Dental abnormalities
• Continued dental abscesses, which may develop into periodontitis or result in tooth loss\(^8\)

References:
10. Skrinar A, Marshall A, San Martin J, Dvorak-Ewell M. X-linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Poster presented at: ENDO 2015; March 5-8, 2015; San Diego, CA.

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This requisition form can be used to submit an order for the Hypophosphatemia Program, a complimentary testing program for genetic hypophosphatemic disorders brought to you by Ultragenyx Pharmaceutical, Inc.

INSTRUCTIONS: Review the ordering options and then complete all sections of this form. Your ordering option will be indicated in the test selection section.

### ORDERING OPTIONS

#### 1. HYPOPHOSPHATEMIA PROGRAM

For individuals that meet the eligibility criteria below and wish to receive the program specific genetic testing panels.

*REQUIRED: You must select below the appropriate eligibility criteria for this patient.*

| Has completed the UltraCare® Start Form for XLH |
| Has a previous diagnosis related to hypophosphatemia* |
| Has a family member with a confirmed XLH diagnosis |
| Exhibits TWO or more of the following clinical signs and/or symptoms (select two or more): |
| Muscle pain, weakness, and/or fatigue |
| Lower limb deformities |
| Fractures/pseudo-fractures |
| Tooth abscesses and/or excessive dental caries |
| Bone, joint pain, and/or joint stiffness |
| Gait abnormalities |

#### 2. GENE-SPECIFIC FAMILY FOLLOW-UP TESTING

For relatives of program participants who received a Pathogenic/Likely Pathogenic result or approved VUS who want to receive gene specific family follow-up testing at no additional charge. Relatives do not need to meet the eligibility criteria listed above. Learn more at www.invitae.com/family.

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### PATIENT INFORMATION

<table>
<thead>
<tr>
<th>First name</th>
<th>MI</th>
<th>Last name</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date of birth (MM/DD/YYYY)</th>
<th>Biological sex</th>
<th>MRN (medical record number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>Black/African American</td>
<td>White/Caucasian</td>
</tr>
<tr>
<td>Hispanic</td>
<td>Native American</td>
<td>Pacific Islander</td>
</tr>
<tr>
<td>Sephardic Jewish</td>
<td>Mediterranean</td>
<td>Other:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Address</th>
<th>City</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone</td>
<td>Email address (report access after clinician releases)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>State/Prov</th>
<th>ZIP/Postal code</th>
<th>Country</th>
</tr>
</thead>
</table>

**Ship a kit to this patient (optional)** by faxing this form to Client Services at 415-276-4164

**Kit type:** Buccal swab kit / Saliva kit

**Ship to:** Address above / Alternate address:

### CLINICIAN INFORMATION

<table>
<thead>
<tr>
<th>Organization name</th>
<th>Phone</th>
<th>Fax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td>City</td>
<td></td>
</tr>
<tr>
<td>State/Prov</td>
<td>ZIP/Postal code</td>
<td>Country</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary clinical contact name (if different from ordering provider)</th>
<th>NPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary clinical contact email address (for report access)</td>
<td></td>
</tr>
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</table>

**Ordering provider (select one ordering provider by marking the checkbox before the name)**

<table>
<thead>
<tr>
<th>Name</th>
<th>NPI</th>
<th>Email address (for report access)</th>
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**Additional clinical or laboratory contacts (optional, to share access to order online)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Email address (for report access)</th>
</tr>
</thead>
</table>

### SPECIMEN INFORMATION

<table>
<thead>
<tr>
<th>Specimen type:</th>
<th>Blood (3-ML purple EDTA) / Buccal Swab / Saliva (Oragene®) / Assisted Saliva</th>
</tr>
</thead>
<tbody>
<tr>
<td>We are unable to accept blood/buccal/saliva from patients with:</td>
<td></td>
</tr>
<tr>
<td>Allergic bone marrow transplants</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion &lt;2 weeks prior to specimen collection</td>
<td></td>
</tr>
</tbody>
</table>

| Specimen collection date (MM/DD/YYYY): |
| If not provided, the day before specimen receipt will be used |

| Special cases: |
| History of current hematologic malignancy in patient |

### POST-TEST GENETIC COUNSELING (please review)

Ultragenyx sponsors post-test genetic counseling, regardless of test result type, at no additional charge to the patient through InformedDNA, an independent genetic counseling service. Please check the box below if you would like InformedDNA to contact your patient for genetic counseling once the patient’s test is complete.

| I authorize Invitae to grant InformedDNA (patientcare@InformedDNA.com) access to the patient’s Invitae record for the purposes of providing genetic counseling services |

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**INVITAE PARTNER CODE**

| XLH |
## Clinical History

**Family History**

<table>
<thead>
<tr>
<th>Relative's relationship to this patient</th>
<th>Maternal or paternal</th>
<th>Diagnosed condition</th>
<th>Age at diagnosis</th>
<th>Relative's relationship to this patient</th>
<th>Maternal or paternal</th>
<th>Diagnosed condition</th>
<th>Age at diagnosis</th>
</tr>
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<tbody>
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</tbody>
</table>

**Personal History**

Is/was this patient affected or symptomatic? Yes No

Provide details in the required clinical history questions (if applicable).

### Clinical History

**Biochemical markers (select all that apply):** It is strongly encouraged to include a copy or the values of abnormal results, when available, for this individual or affected family members. This information is useful for variant interpretation.

- Reduced serum phosphate (<LLN)
- Reduced TmP/GFR (<LLN)

### Optional - Requested Variants for this Patient's Report, if Known

To have the presence or absence of specific variants commented on in this patient’s report, provide the details below. For gene-specific family follow-up see Note under Test Selection.

- Was the proband (individual with variant) tested at Invitae? Yes Invitae Order ID: RQ# No: Attach copy of test results (required)

- Variant(s) (e.g. GENE c.2200A>T (p.Thr734Ser) NM_00012345) If left blank, all variants identified in the proband will be commented on.

### Test Selection – Select option 1 or 2 below:

1. **Hypophosphatemia Program**

   - Indicate test(s) to be performed below:

<table>
<thead>
<tr>
<th>Test code</th>
<th>Test name</th>
<th># of genes</th>
<th>Gene list</th>
</tr>
</thead>
<tbody>
<tr>
<td>72039</td>
<td>Invitae Hypophosphatemia Panel</td>
<td>17</td>
<td>ALPL, CLCN5, CTNS, CYP2R1, CYP27B1, DMP1, ENPP1, FAH, FAM20C, FGFR2, FGFR1, GNAS, OCRL, PHEX, SLC34A1, SLC34A3, VDR</td>
</tr>
</tbody>
</table>

2. **Gene-Specific Family Follow-up Testing**

   - For relatives of a program participant ("proband") who received a Pathogenic/Likely Pathogenic result or approved VUS.

   - Proband’s Invitae Order ID: RQ#

   - This patient’s relationship to proband:

     - Parent
     - Sibling
     - Grandchild
     - Child
     - Self
     - Other:

   - Gene(s) to be tested in this patient:

   - NOTE: The presence or absence of all variants identified in the proband for the gene(s) ordered for gene-specific family follow-up will be commented on in this patient’s report unless a limited selection is specified in the Requested Variants section above. Invitae will report any Pathogenic/Likely Pathogenic variants found in this patient for the gene(s) ordered.

   - Invitae continually updates its panels on the basis of recent evidence. If an order is placed using an outdated test requisition form, Invitae reserves the right to upgrade ordered tests to their current versions. Test IDs containing add-on codes will include the original panel as well as the add-on.

   - By signing this form, the medical professional acknowledges that the individual/family member authorized to make decisions for the individual (collectively, the “Patient”) has been supplied information regarding and consented to undergo genetic testing, substantially as set forth in Invitae’s Informed Consent for Genetic Testing (www.invitae.com/forms). In connection with the Program the Patient has been informed that Invitae may notify them of clinical updates related to genetic test results (in consultation with the ordering medical professional as indicated) and has been informed that de-identified Patient data may be used and shared with third parties, for research and commercial purposes and, in the U.S., to contact their medical professional. For orders originating in Canada, the Patient has been informed that their personal information and specimen will be transferred to and processed in the U.S. and that de-identified Patient data may be used and shared for research and commercial purposes in the U.S. The medical professional warrants that he/she will not seek reimbursement for this no-charge test from any third party, including but not limited to federal healthcare programs. The medical professional also hereby acknowledges that organization and clinician contact information provided in the order may be shared with third parties, including commercial organizations, that may contact the medical professional directly in connection with the Program, and that they have made the Patient aware that de-identified Patient data may be used and shared with such third parties, for purposes which include contacting their medical professional directly in connection with the Program. A list of third party partners may be provided upon request. I attest that I am authorized under applicable state law to order this test.

   - Medical professional signature (required)

   - Date (MM/DD/YYYY)