Study Protocol

Bone Age Prediction Hand X-ray

as part of Project AIR

1. **Objective**
   Validate and compare the stand-alone diagnostic performance of commercial artificial intelligence (AI) based software for the bone age prediction from radiographs of the left hand in a clinical pediatric population.

2. **Study design**
   An ongoing retrospective study in which commercial AI software is being validated on a dataset from multiple centers. Vendors make their algorithm temporarily available to the researchers to generate the results. The data will not be shared with the vendors. Reader studies on the same dataset are performed by radiologists to provide context to the stand-alone software performance.

3. **Study population**
   - **3.1. Inclusion criteria**
     - Centers: Academic, non-academic
     - Patient age: 0-18 years old
     - Posterior anterior (PA) left hand radiograph
     - Maximum one study per subject
   - **3.2. Exclusion criteria**
     - Low quality imaging
     - Right hand radiographs
   - **3.3. Sample size**
     - Data will be collected from at least four centers in Europe, with a minimum of 50 samples per center.
     - Initial target: 300 samples
     - Consecutive series

4. **Possible investigational products**
   Preliminary selection of products that are potentially eligible for this study. We welcome feedback about additional products.
   - ImageBiopsy Lab - IB Lab PANDA
   - Visiana - BoneXpert

- VUNO Med® - BoneAge™

5. Methods

5.1. Study parameters

5.1.1. Metrics

- Mean absolute error
- Mean error
- Accuracy. The prediction is deemed correct when maximally deviating ± 6 months from the reference standard.

5.1.2. Subgroup analysis

Subanalysis is performed for e.g. age groups, gender, race and X-ray manufacturer

5.1.3. Not-processed-rate

5.2. Data collection

5.2.1. Imaging data

- DICOM file of pediatric hand radiograph

5.2.2. Clinical data

- Center: coded
- Patient age (chronological): years and months
- Bone age: years and months
- Gender: M/F
- Acquisition machine brand: coded
- Acquisition date: years
- Race: categorial
- Diagnosis:
  - Normal
  - Genetic or hereditary disorder
    Turner syndrome, Down syndrome, Prader- Willi syndrome, Noonan syndrome, Williams syndrome, CHARGE (coloboma of the eye, heart defect, atresia of the choanae, retardation of growth, and ear abnormalities) syndrome, Rubinstein-Taybi syndrome, and Kallmann syndrome, hypochondroplasia (Short stature)
  - (Hereditary) metabolic disorder
    Obesity, dyslipidemia, Malnutrition, Crohn disease, Insulin resistance, glycogen storage disease, Vitamin deficiencies (rickets), glutaric aciduria, methylmalonic acidemia
  - Hormonal disorder
    Growth hormone deficiency, Hypothyroidism, Congenital adrenal, Delayed puberty and hypogonadism hyperplasia, Sexual precocity, Gigantism, suprasellar germinoma

5.3. Reference standard

Average of Greulich-Pyle atlas-based bone age provided by three pediatric or musculoskeletal radiologists individually. Cases with a strong disagreement (± 1 year difference) were reevaluated until consensus was reached.

5.4. Software prediction outcome

5.4.1. Bone age in years and months, Greulich-Pyle method (subject's sex is provided)

5.5. Reader study questions

5.5.1. Bone age in years and months, Greulich-Pyle method (subject's sex is provided)

6. Statistical analysis

6.1. Comparing with average readers

- Confidence intervals, Bonferroni-corrected non-inferiority analysis.