

Closing the Gaps in Pediatric Reference Intervals for Biomarkers of Health & Disease:

The CALIPER Program

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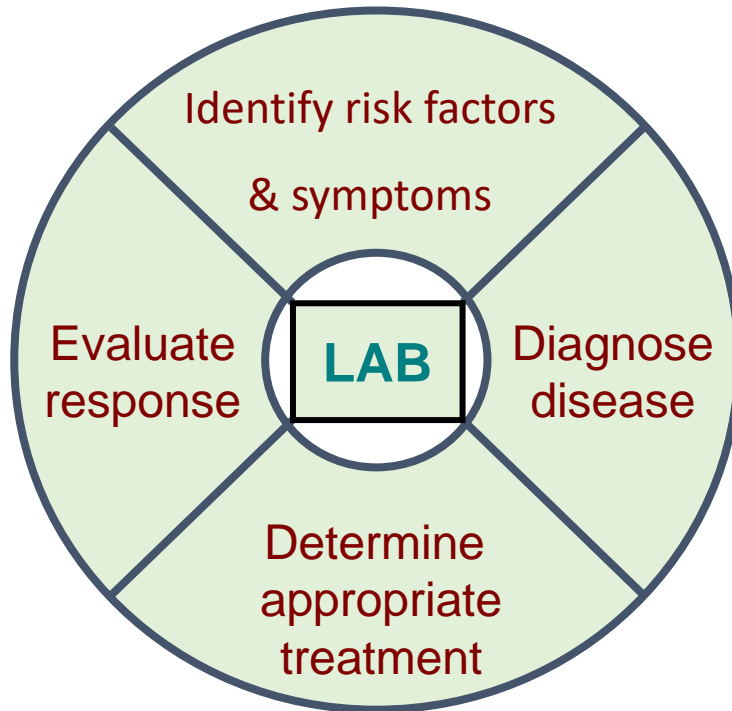
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Toronto, ON, Canada



Critical Role of Laboratory Medicine in Healthcare Delivery



Laboratory Medicine is part of the multi-disciplinary team at the centre of healthcare



The quality of the Clinical Laboratory Service is critically dependent on:

- **Quality Lab Operations**
Accurate/Precise Testing Process (validated methods/systems)
- **Appropriate Reference Intervals/Decision Limits**
Accurate interpretation of lab results based on appropriate reference intervals or decision limits

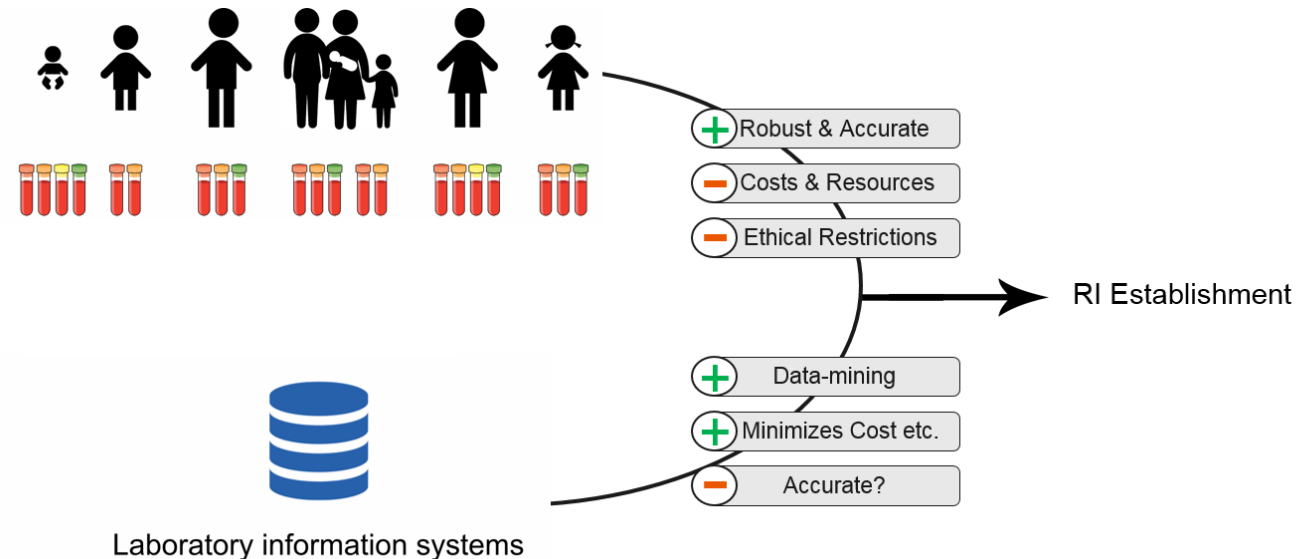
Key to ensuring Postanalytical Quality of Laboratory Reports

Laboratory Medicine and Clinical Decision Making: *Reference Intervals*

- **Reference Intervals:** health associated benchmarks that assist in clinical decision-making and are defined as the 2.5th and 97.5th percentiles established in a healthy reference population
- **Methods for establishing reference intervals::**

Direct Method: Involves recruiting healthy subjects into a study in which samples are collected for the sole purpose of determining a reference interval

Indirect Method: Involves using results of a database established for another purpose (i.e. laboratory information systems)



Laboratory Medicine in Patient Care: *Critical Evidence Gaps*

- Due to the extensive resources required for reference interval establishment, critical gaps in reference intervals continue to exist in specific populations:

Pediatrics

Challenges:

- Difficult to recruit large pediatric populations
- The need for many partitions due to growth and development throughout childhood

Covariates to consider:

- Chronological age & sex
- Tanner stage, BMI, and ethnicity

Current gaps:

- Neonates, infants and young children

Pregnancy

Challenges:

- Can be difficult to recruit large maternal populations
- Increasing need for many partitions due to development throughout pregnancy

Covariates to consider:

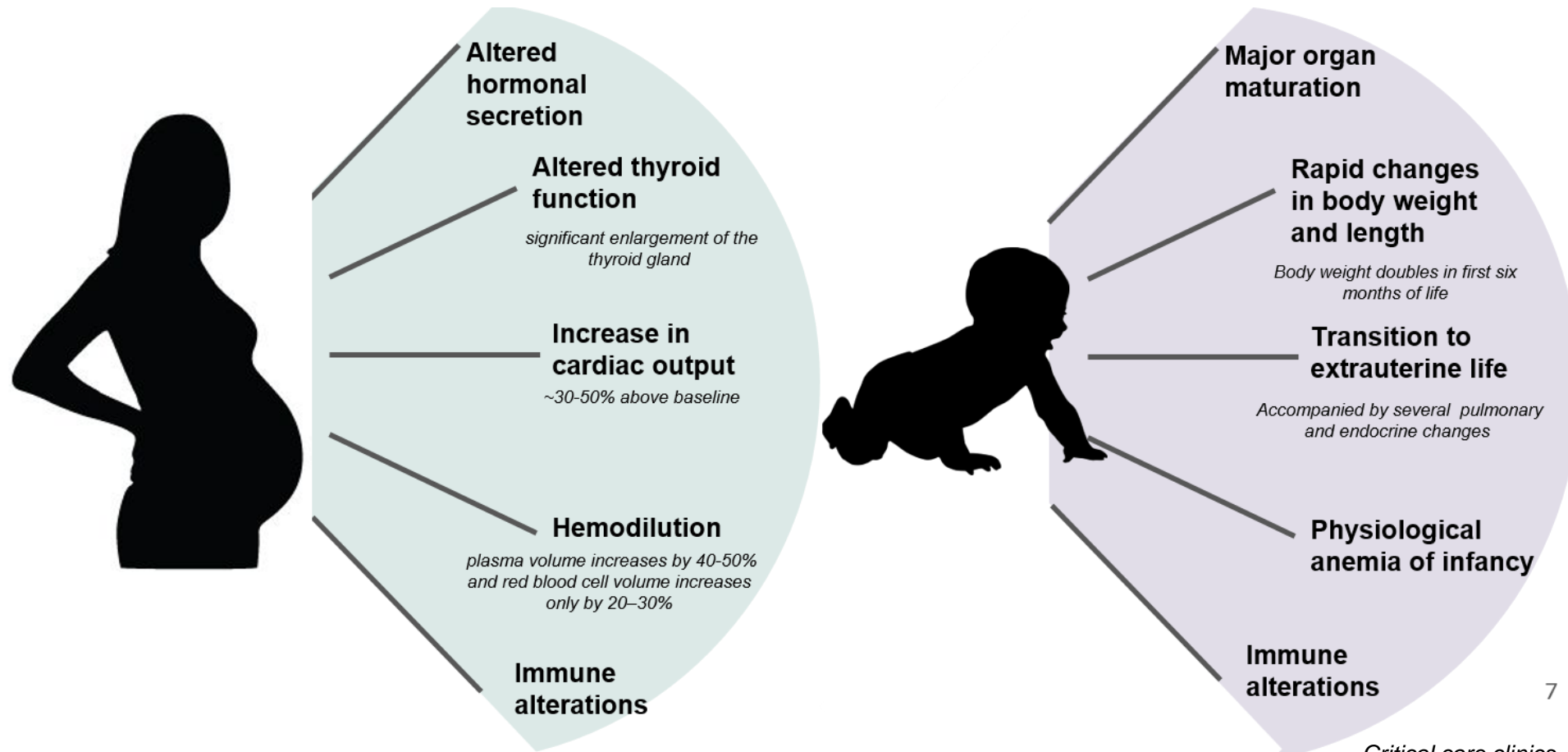
- Chronological age
- Gestational age, BMI, and ethnicity

Current Gaps:

- Data is based mostly on small samples, outdated analytical platforms, other populations

Major Physiological Changes in Pregnancy and Early Infancy

A comprehensive and robust database for the interpretation of laboratory test results in pregnancy and infancy is essential, allowing for more accurate clinical decision-making and improved health outcomes



7

Critical care clinics. 2004 Oct 1;20(4):609-15

Children are NOT small adults




- **Body weight:**
 - Doubles by 6 months of age
 - Triples by the first birthday
- **Body length** increases by 50% during the first year
- **Major organ systems** grow and mature
- Important changes take place during **puberty**
 - Accelerated growth and sexual maturation occur



Pediatric Reference Intervals Need to reflect differences in:

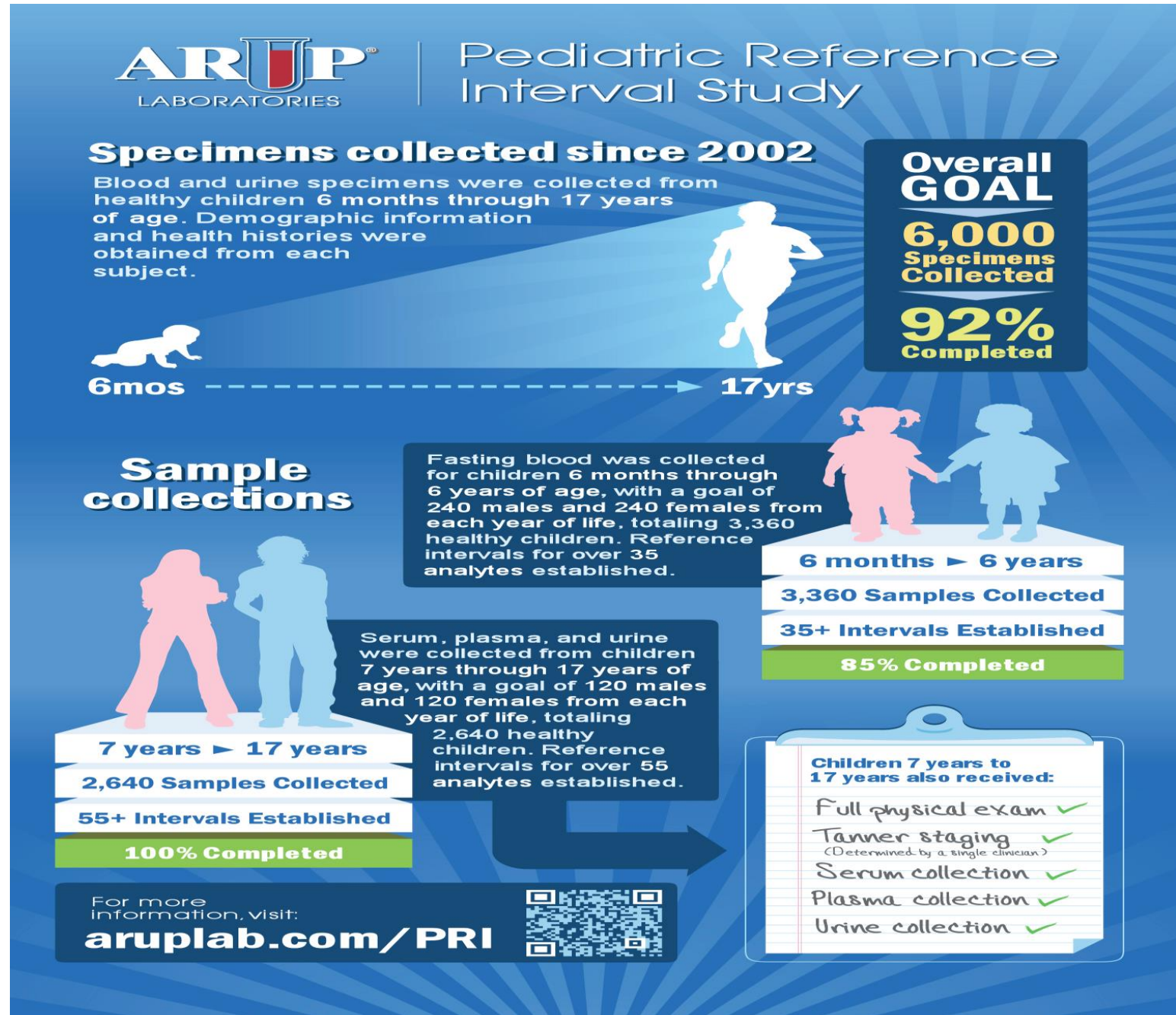
- Development & physiologic function at different ages
- Key covariates including gender, age, BMI, sexual development (Tanner stage), and ethnicity

Global Reference Interval Initiatives in Pediatrics

Study	Country	Age Range (years)	Sex	Statistical Method	Examples of Groups of Biomarkers Studied
AACB	Australia and New Zealand	All age groups	Both	Central 95%	Common blood analytes (mostly ions and enzymes)
CALIPER	Canada 	0-18	Both	Central 95%	Common biochemical markers Endocrine markers Tumor markers Vitamins Metabolic disease biomarkers Testosterone indices
CHILDX	United States 	0.5-17	Both	Median, mean and central 95%	Enzymes Coagulation tests Hormones Vitamins Bone markers
COPENHAGEN	Denmark	5-20	Both	Central 95%	Common blood analytes
KIGGS	Germany 	0-18	Both	Median and central 90%	Nutrient deficiency markers Non-communicable diseases and lipids Immunology markers Thyroid hormones
LOOK	Australia	8, 10 and 12	Both	Median and central 95%	Cardiac Biomarker Common blood analytes

CHILDX Study (USA)

(ARUP Laboratories)





Aimed to collect blood samples from around 5000 children between birth and 18 years, so we can establish normative data for age appropriate reference intervals in haematology, immunology, and biochemistry for the paediatric population for RCH and for laboratories throughout the state of Victoria.

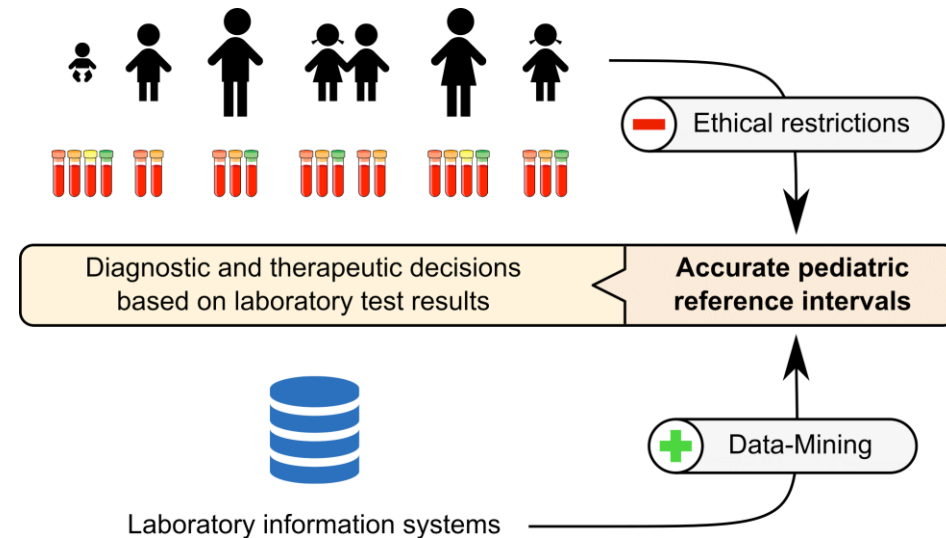


<https://www.pedref.org/index.html>

Indirect Reference Interval Calculation using Patient Data (TML Statistical Method)

The PEDREF study

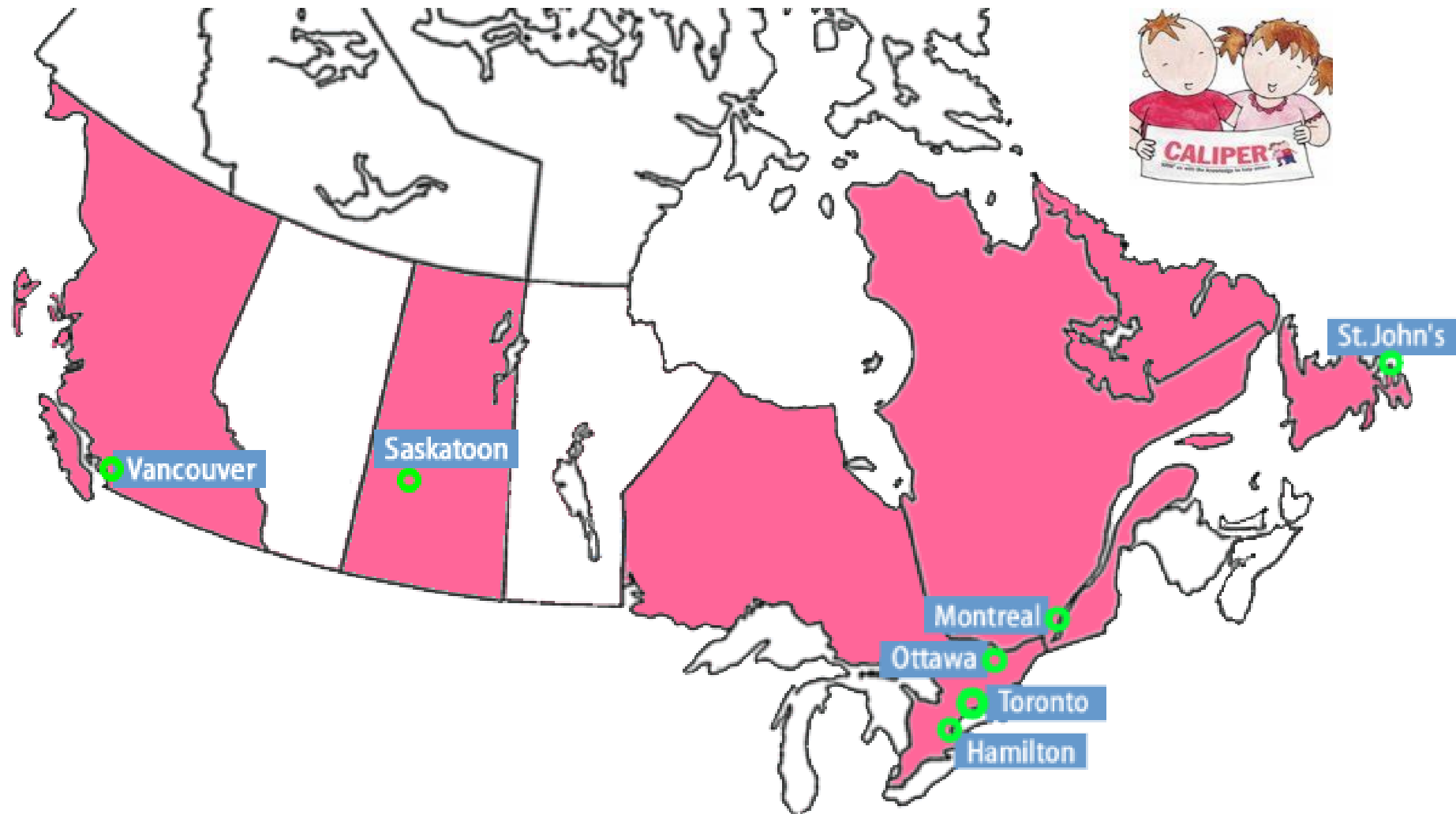
- Improving children’s health assessment using data-mining of laboratory information systems — the multi-center PEDREF study to create next-generation reference intervals for laboratory analytes in pediatrics
- Access the web application accompanying our publication Next-generation reference intervals for pediatric hematology.



PRINCE Study in China



CALIPER Initiative in Canada



CALIPER Initiative in Canada

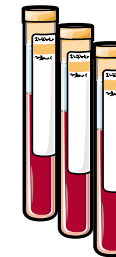
CALIPER = **C**anadian **L**aboratory **I**nitiative on **P**ediatric **R**eference Intervals

- Nation-wide initiative to improve the diagnosis and care of children, in children hospitals and healthcare centres across Canada and globally
- Main Objectives:
 1. To develop **a comprehensive database** of covariate stratified reference intervals
 2. To determine the **effects of key covariates (age, sex, ethnicity, BMI)** on laboratory reference intervals in healthy children and adolescents
 3. To **disseminate new reference data** to pediatric healthcare community worldwide via novel knowledge translation tools (WebApp & Mobile App)

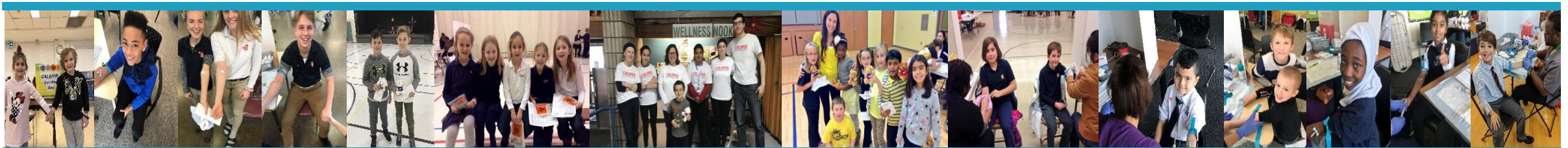


CALIPER: A Canadian Initiative to Close the Evidence Gap in Pediatric Reference Intervals for Biomarkers of Health & Disease

- **CALIPER (CANADIAN LABORATORY INITIATIVE ON PEDIATRIC REFERENCE INTERVALS):** A CIHR Funded Initiative (2010-present)
- **OBJECTIVE:** To establish *a comprehensive database of healthy reference standards for biomarkers of health and disease in children and adolescents.*
- **STUDY COHORT:** >12000 Children and adolescents (birth to 18 years) recruited over the past decade through various **community-based programs** including:
 - *Schools*
 - *Community Centre*
 - *Art & Sport events and festivals*
- **STUDY BIOBANK:** Pediatric biobank of collected serum specimens (-80C)



www.caliperdatabase.org
www.caliperproject.org



CALIPER Initiative: *Recruitment*



Recruitment

- *Community centers*
- *Schools*
- *Day Cares*
- *Summer Camps*

Promotional Materials:

- *Information packages*
- *Brochures*
- *Postcards*



CALIPER Community Clinics



CALIPER Participants



CALIPER Participants





CALIPER Participants



CALIPER Website

Brand new website now live!

www.caliperproject.ca
www.caliperproject.org

- **New information for:**
 - Participants and families
 - Community partners
 - Healthcare professionals
- Learn more about current work and ongoing substudies
- Information on our processes for pediatric reference intervals is also provided!

<p>Pregnancy & Infancy</p>  <p>The Mother & Child Health Initiative aims to establish a comprehensive database of healthy reference intervals for blood tests in pregnant women.</p> <p>Learn about the Mother and Child Health Initiative</p>	<p>COVID-19</p>  <p>The COVID-19 Seroprevalence Study aims to monitor antibody levels after COVID-19 vaccination in children and adults.</p> <p>Learn about the COVID-19 Seroprevalence Study</p>	<p>Early Childhood</p>  <p>The CALIPER Early Childhood Study aims to develop more accurate reference intervals for young children who are 0-5 years of age.</p> <p>Learn about the Early Childhood Study</p>	<p>Obesity & Metabolism</p>  <p>The Lipid Metabolism in Adolescents Study aims to examine lipid metabolism biomarkers in adolescents with insulin resistance and obesity.</p> <p>Learn about the Lipid Metabolism in Adolescents Study</p>
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SickKids

[Welcome](#) [Our History](#) [Children & Families](#) [Community Partners & Volunteers](#) [Healthcare Professionals](#) [CALIPER Database](#) [Contact Us](#)



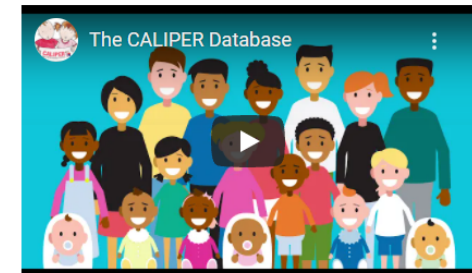
Welcome to CALIPER

CALIPER
'ARM' us with the knowledge to help others

The **Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER)** is a nation-wide health initiative to improve the diagnosis and monitoring of children and adolescents with medical concerns. Our main objective is to establish a **comprehensive database** of reference intervals for blood test results in children and adolescents. CALIPER is designed to fill the gaps that currently exist in accurately interpreting blood test results with the ultimate goal of **improving the care of children** at SickKids and other children's hospitals around the world. Since 2009, we have made great **progress**, including:

- ✓ Recruited **+12,000 healthy children** and adolescents from schools and other community centres
- ✓ Established paediatric reference intervals for **+185 laboratory biomarkers** of health and disease
- ✓ Published **+50 peer-reviewed papers** in high-impact journals to share methods and data worldwide
- ✓ Created an **online database and mobile application** for free access to CALIPER reference intervals

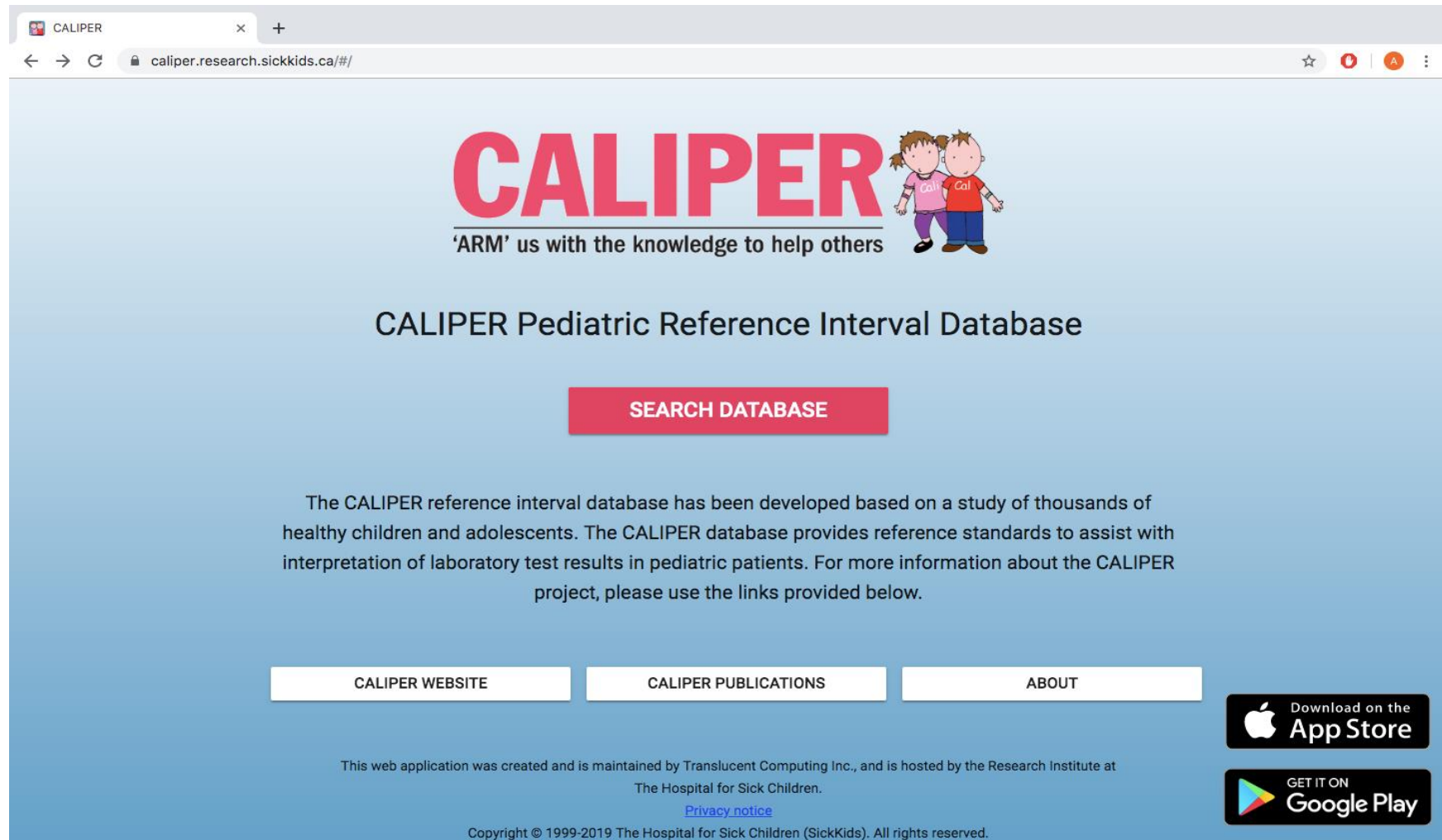
CALIPER would not be possible without the collaboration of **community partnerships** as well as our CALIPER participants and volunteers. Thank you!



CALIPER Promotional Video

CALIPER Database of Pediatric Reference Intervals

The CALIPER Web App has been developed for laboratory specialists, paediatricians, family physicians, other healthcare workers



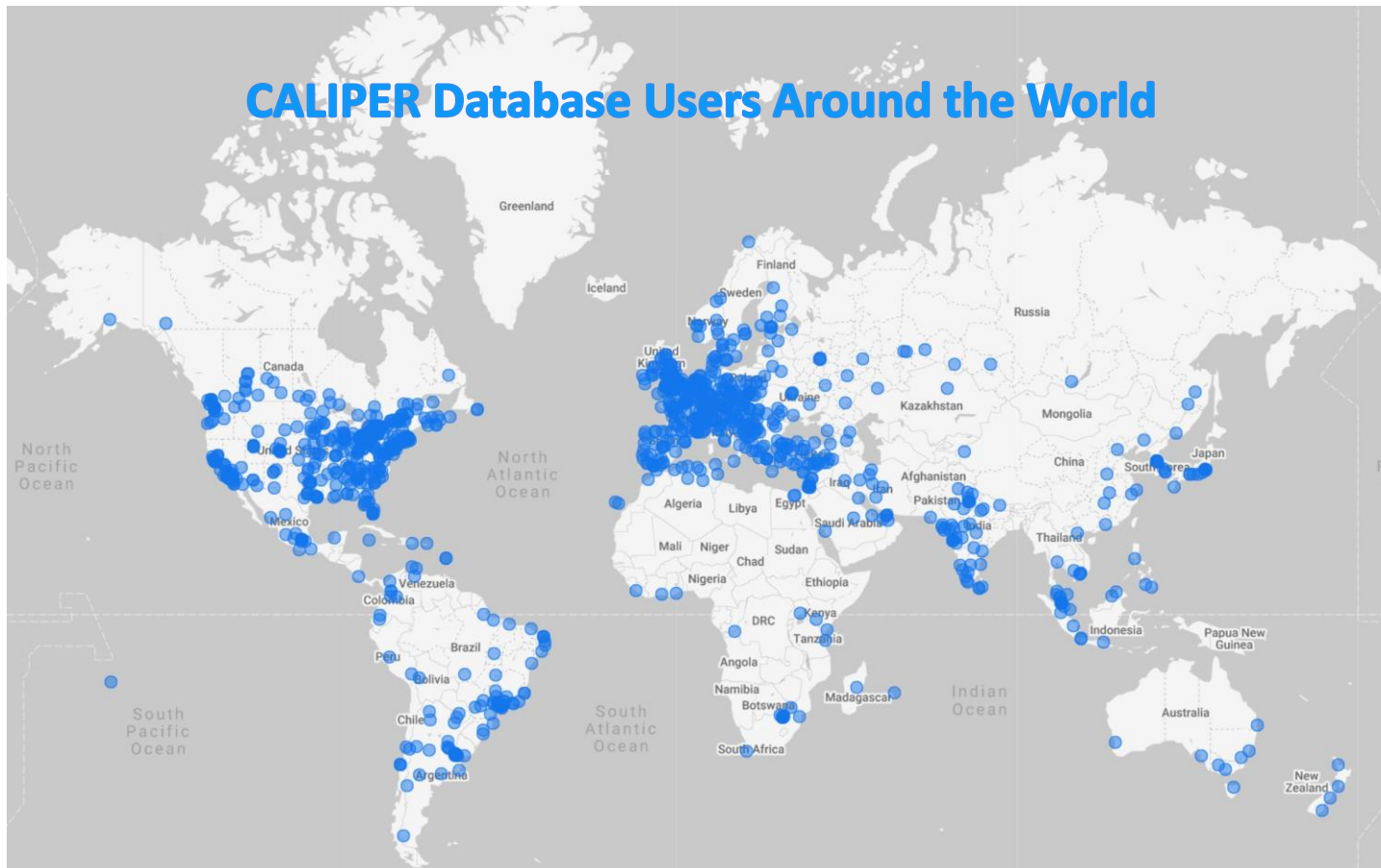
The screenshot shows the CALIPER website interface. At the top, the browser address bar displays 'caliper.research.sickkids.ca/#/'. The main heading is 'CALIPER' in large red letters, followed by the tagline ''ARM' us with the knowledge to help others' and an illustration of two children. Below this is the title 'CALIPER Pediatric Reference Interval Database' and a prominent red button labeled 'SEARCH DATABASE'. A paragraph of text explains the database's development based on a study of thousands of healthy children and adolescents. At the bottom, there are three white buttons: 'CALIPER WEBSITE', 'CALIPER PUBLICATIONS', and 'ABOUT'. In the bottom right corner, there are logos for 'Download on the App Store' and 'GET IT ON Google Play'. A footer contains copyright information: 'Copyright © 1999-2019 The Hospital for Sick Children (SickKids). All rights reserved.'

A user friendly and easy tool to view latest reference value database developed based on thousands of healthy and ethnically diverse children and adolescents.

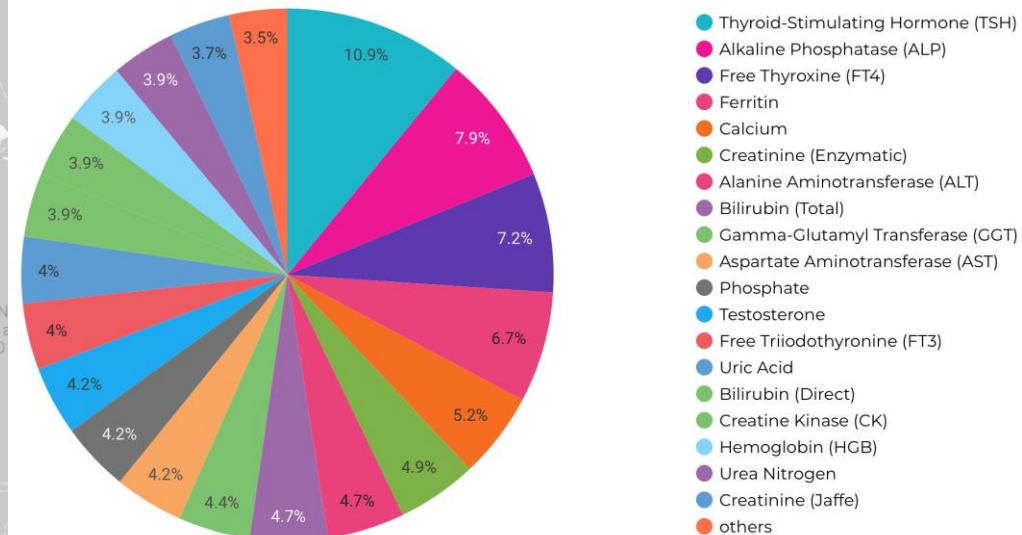
CALIPER Database *Global Reach*

Pediatric reference intervals available for over **200 laboratory biomarkers** on several analytical platforms based on data from thousands of healthy children and adolescents from birth to 18 years

CALIPER online database currently has over **5,000 registered users** from **3,650 institutions in 100 countries**



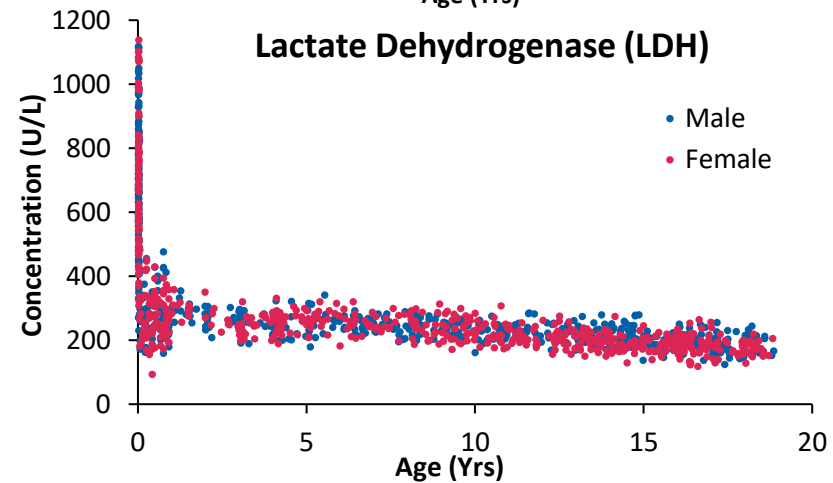
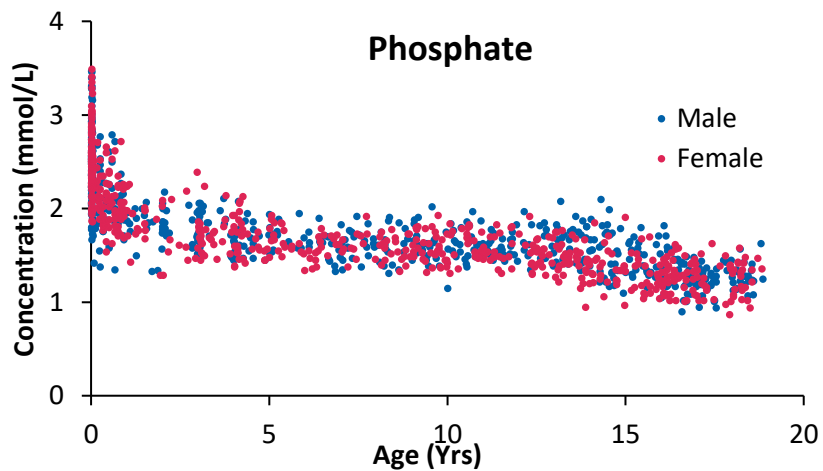
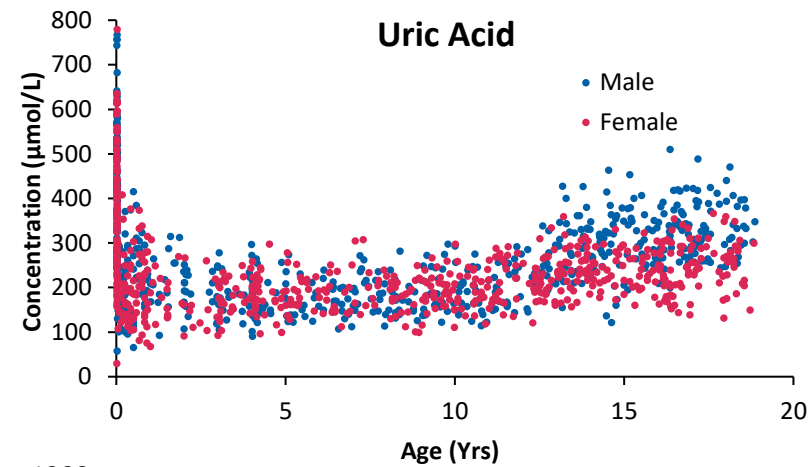
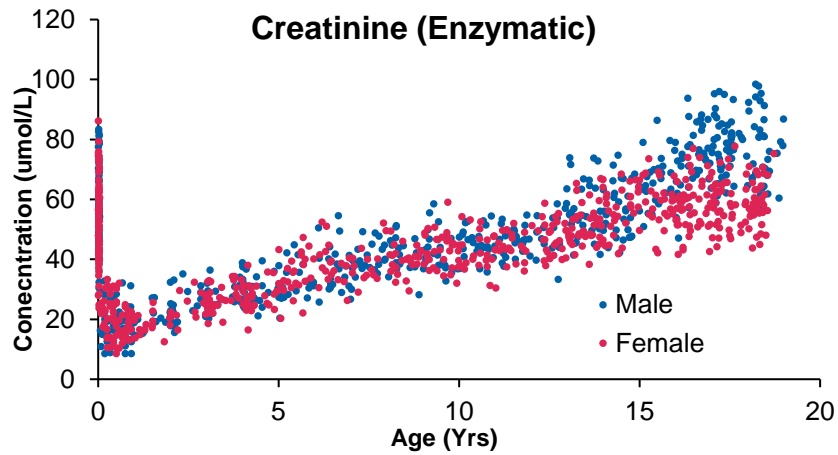
www.caliperdatabase.org



Most Popular Medical Lab Tests Searched in CALIPER Database

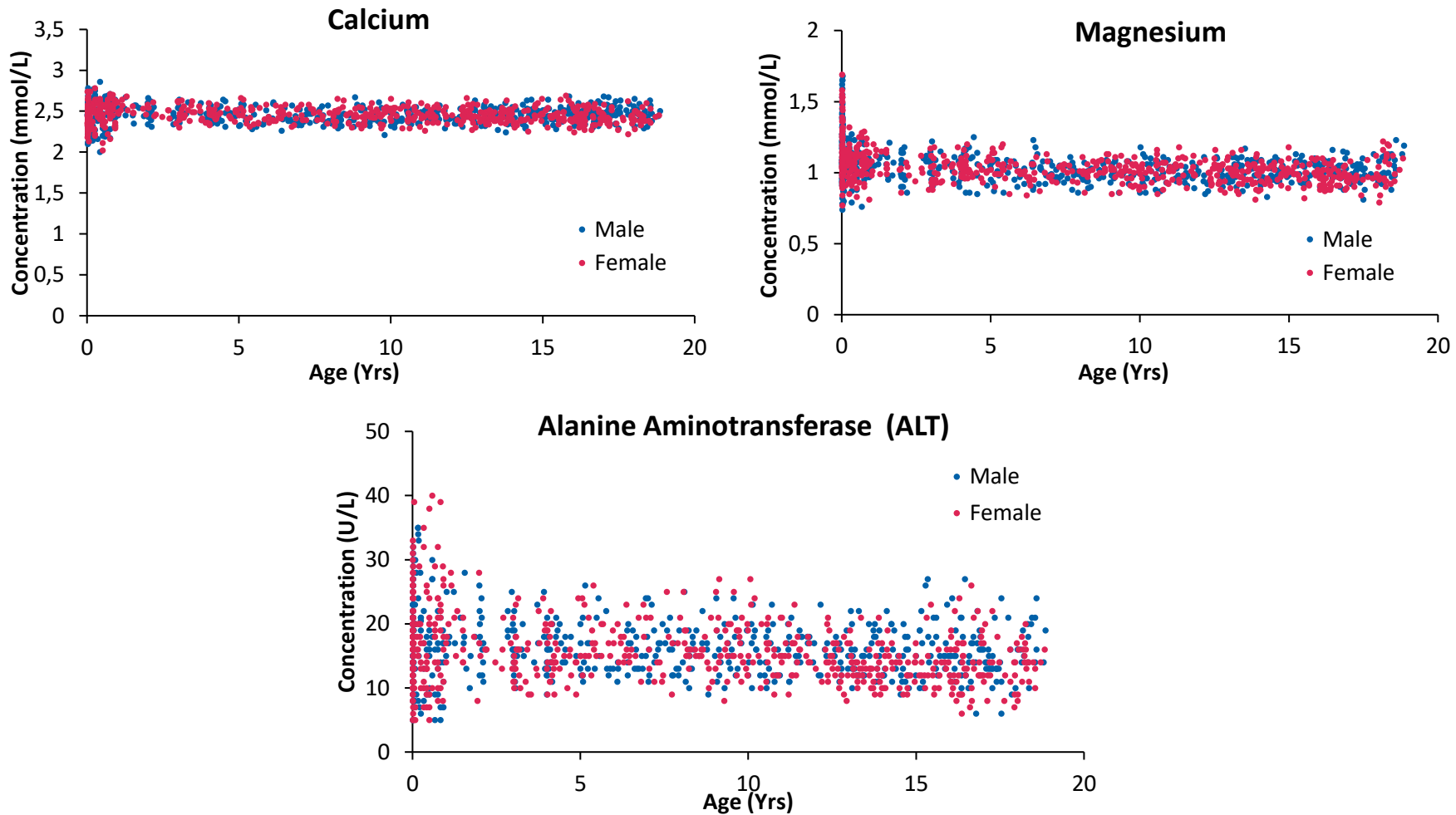
CALIPER Reference Database

Increasing & Decreasing Trends Across the Pediatric Age Range



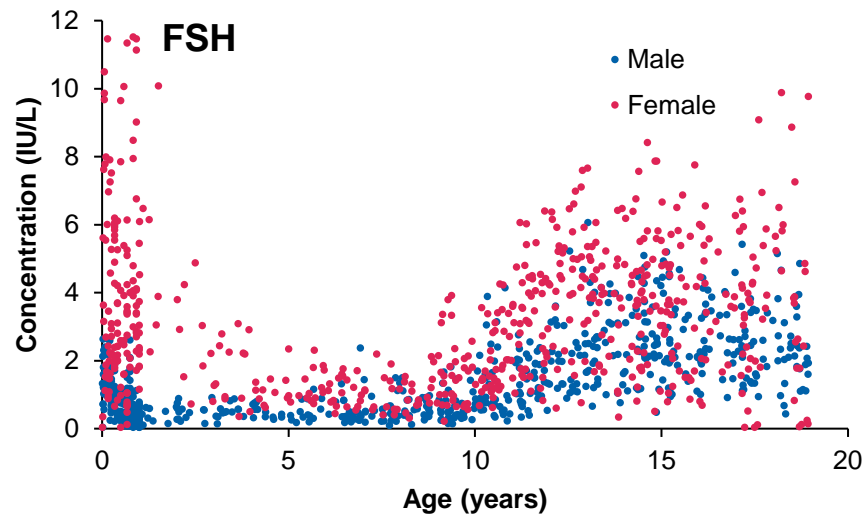
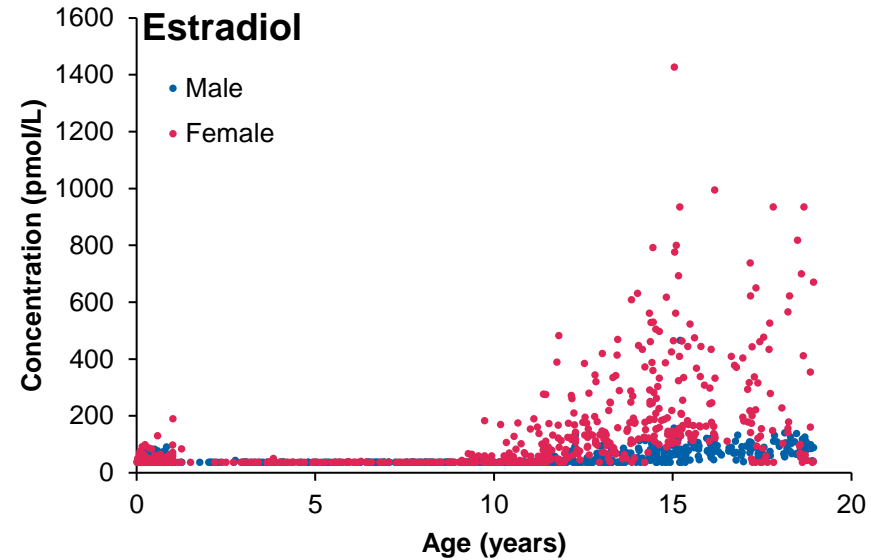
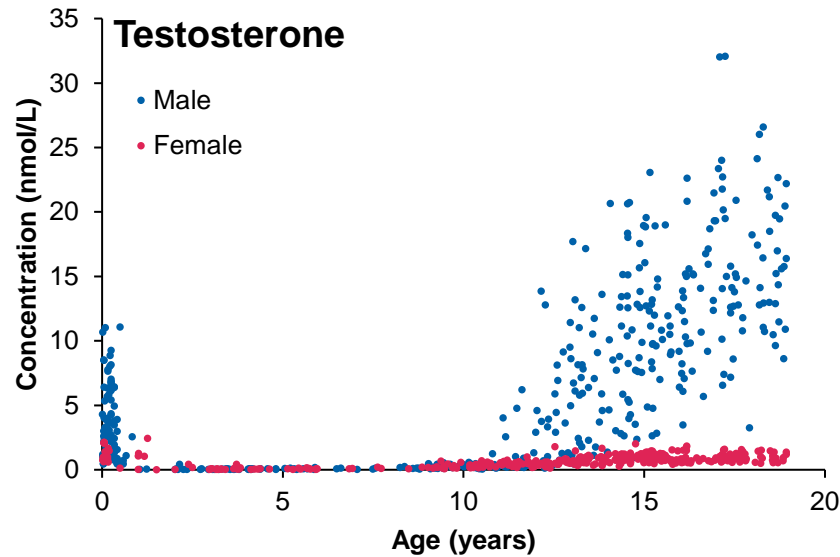
CALIPER Reference Database

Consistency Across the Pediatric Age Range



CALIPER Reference Database

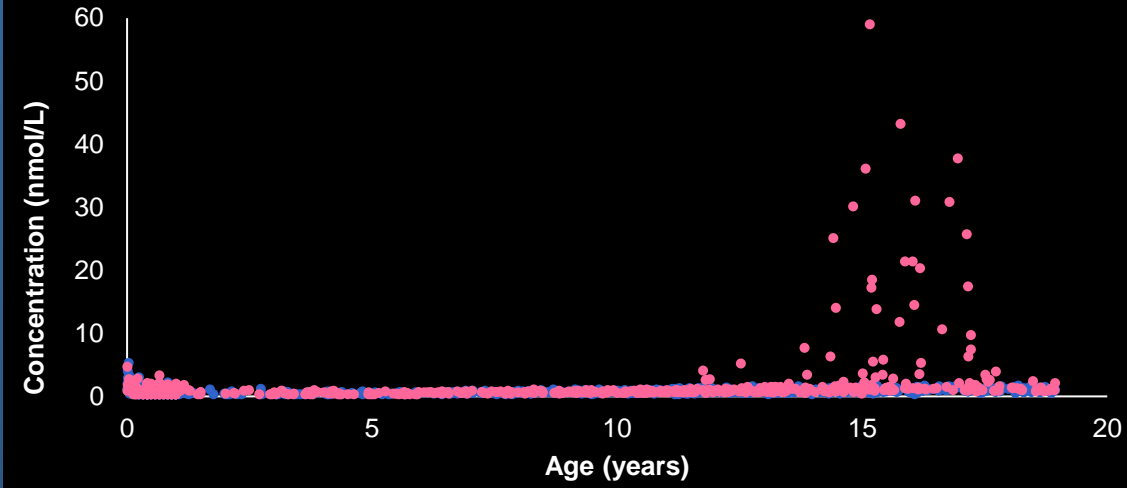
Sex-Specific Observed Across the Pediatric Age Range



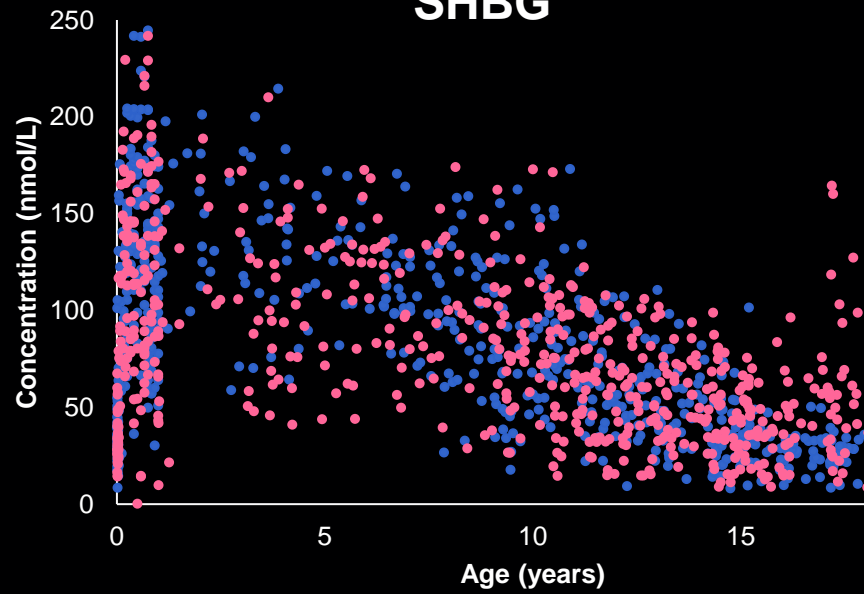
*Stratified by Age, Sex,
& Tanner Stage*

Clinical Chemistry 2013

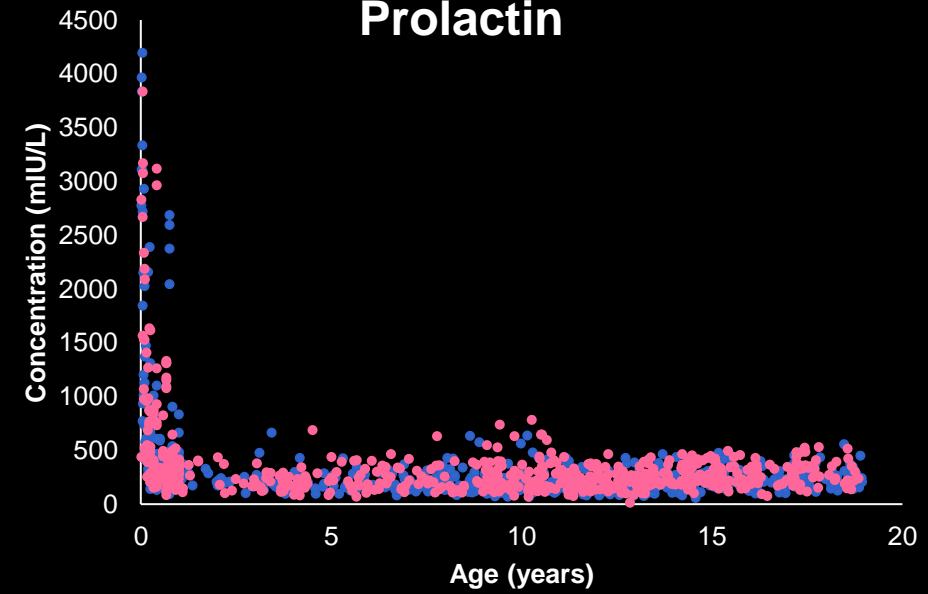
Progesterone



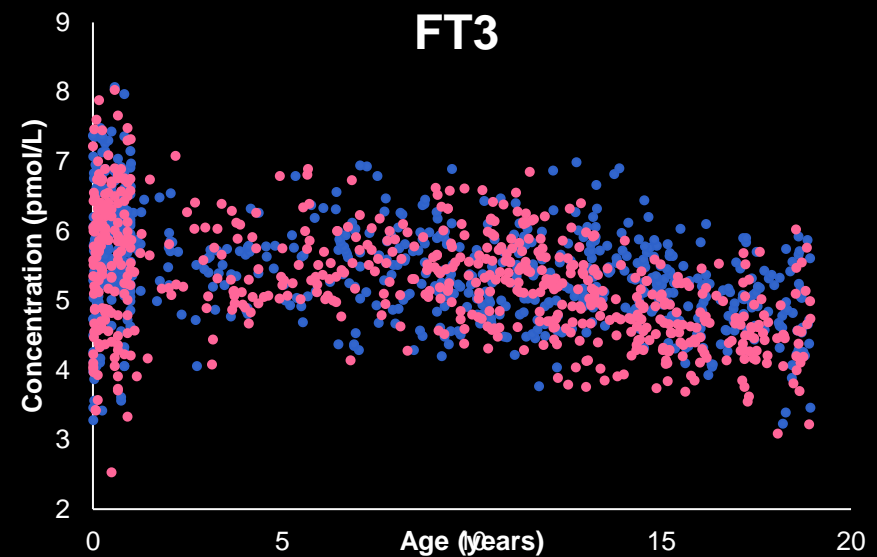
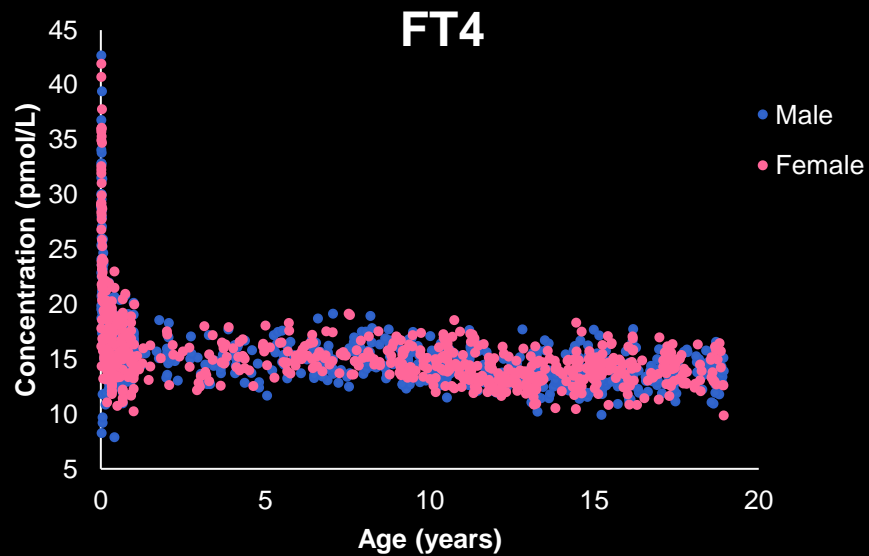
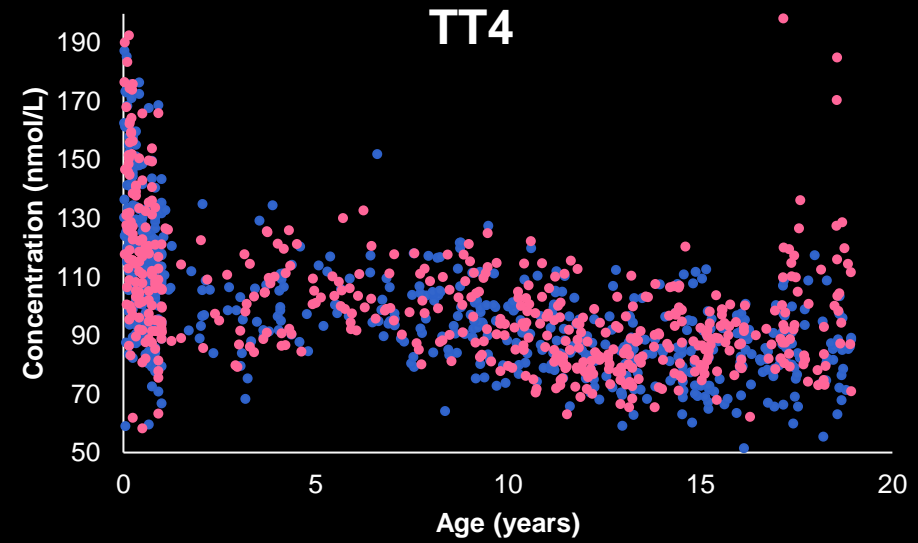
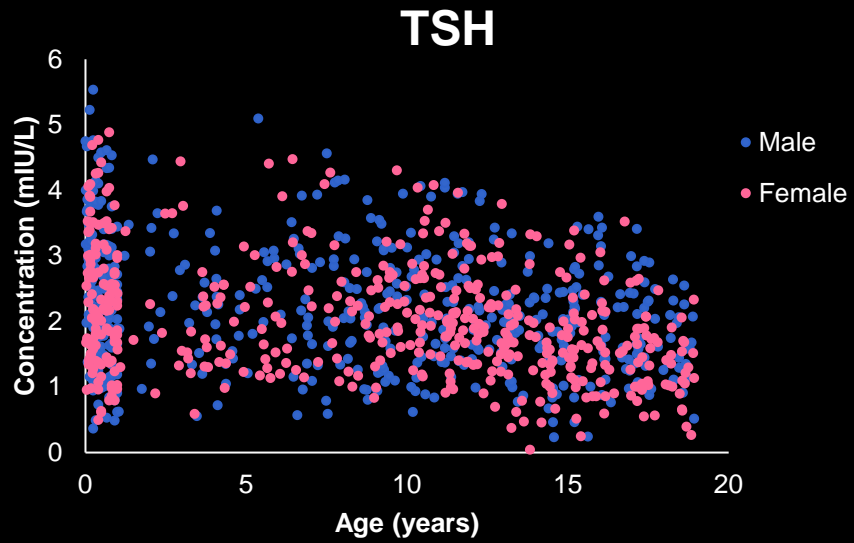
SHBG

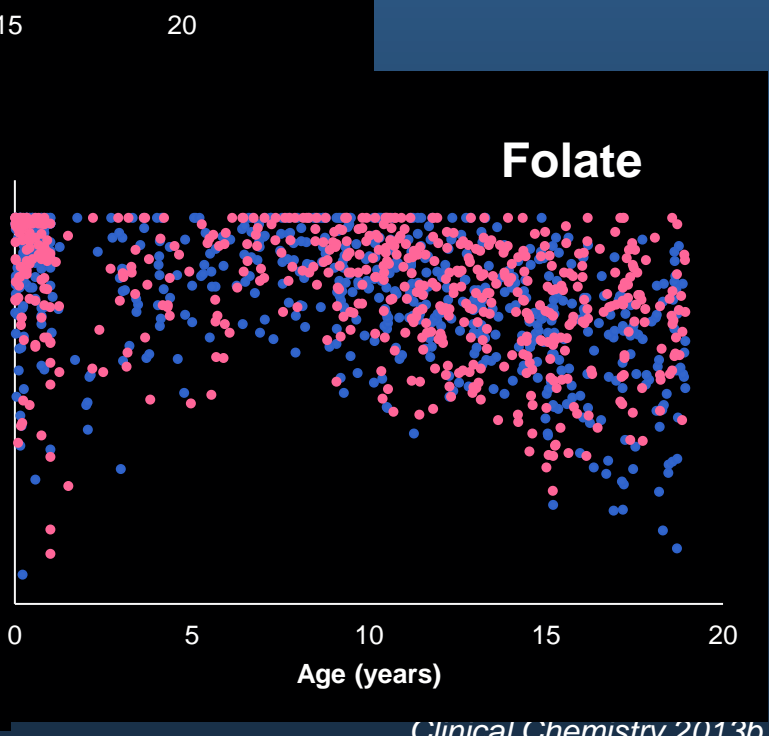
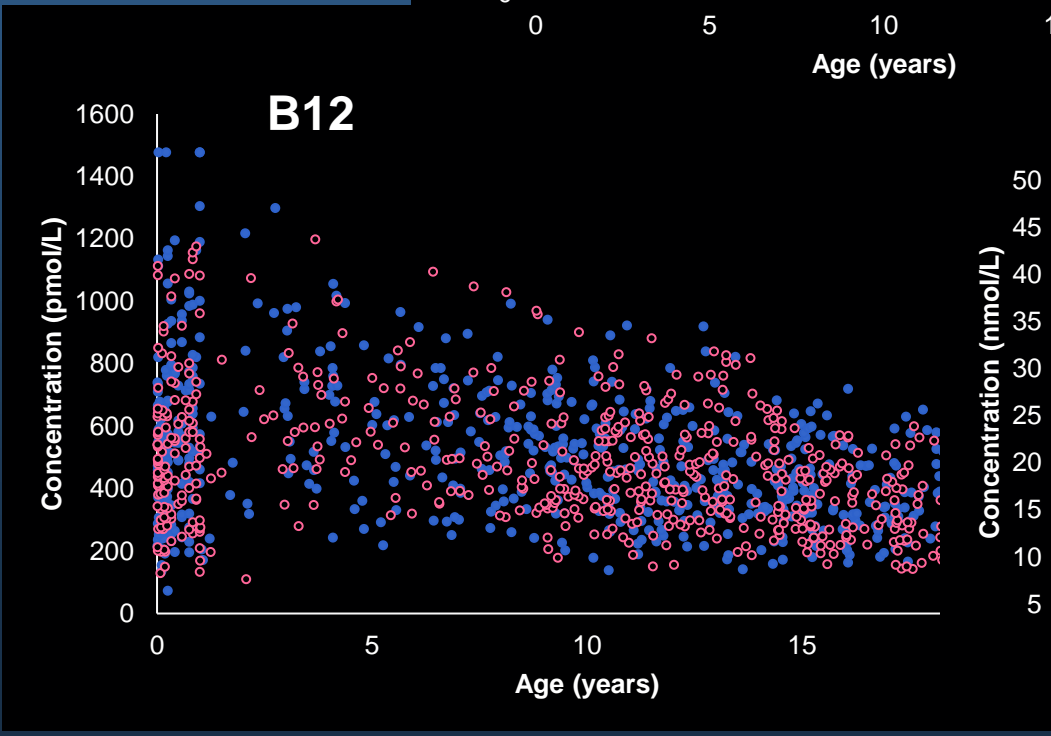
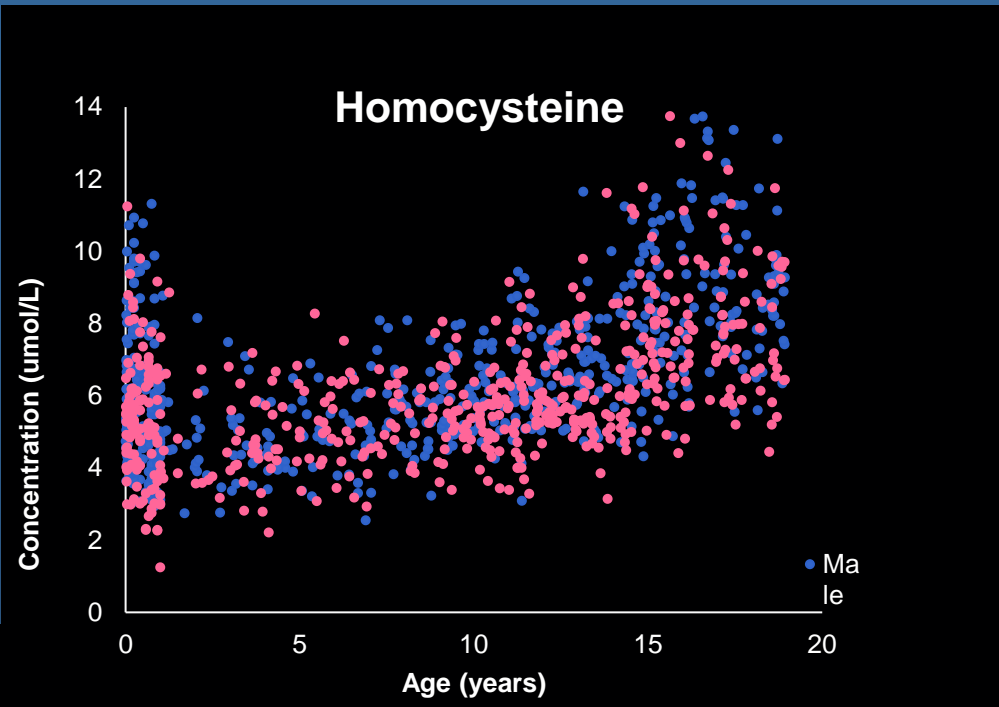


Prolactin

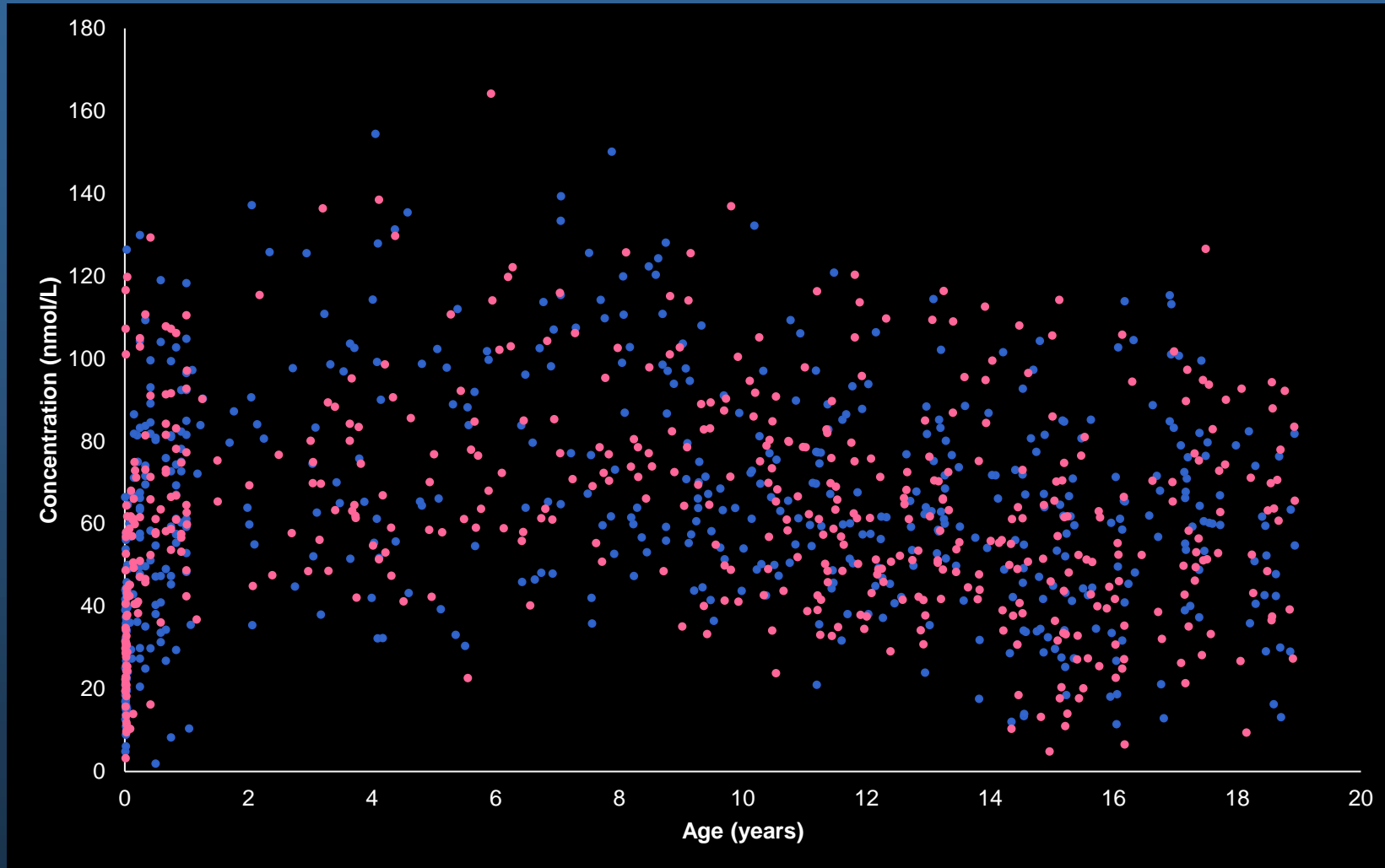


Thyroid Hormones

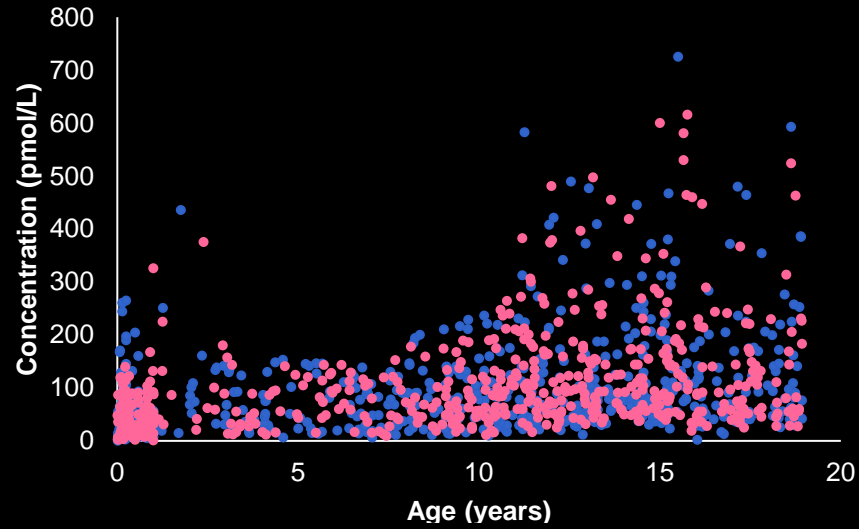




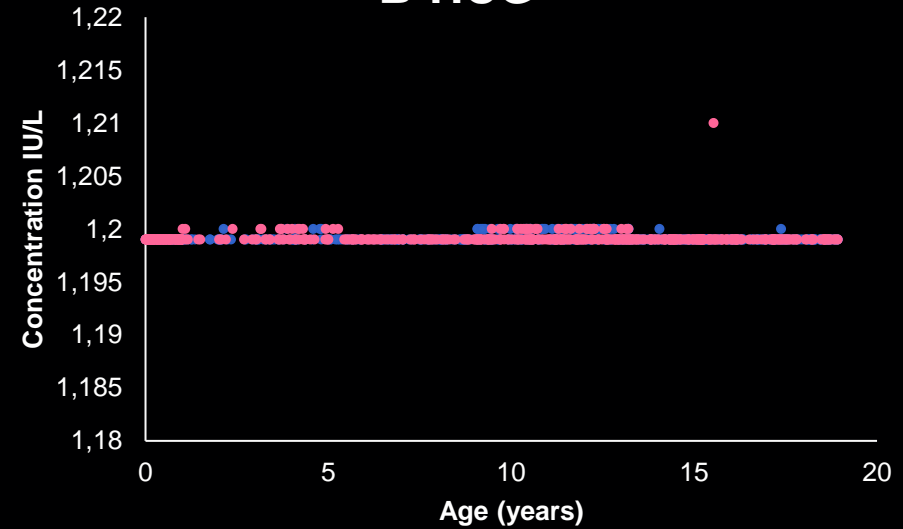
Vitamin D (25 OH)



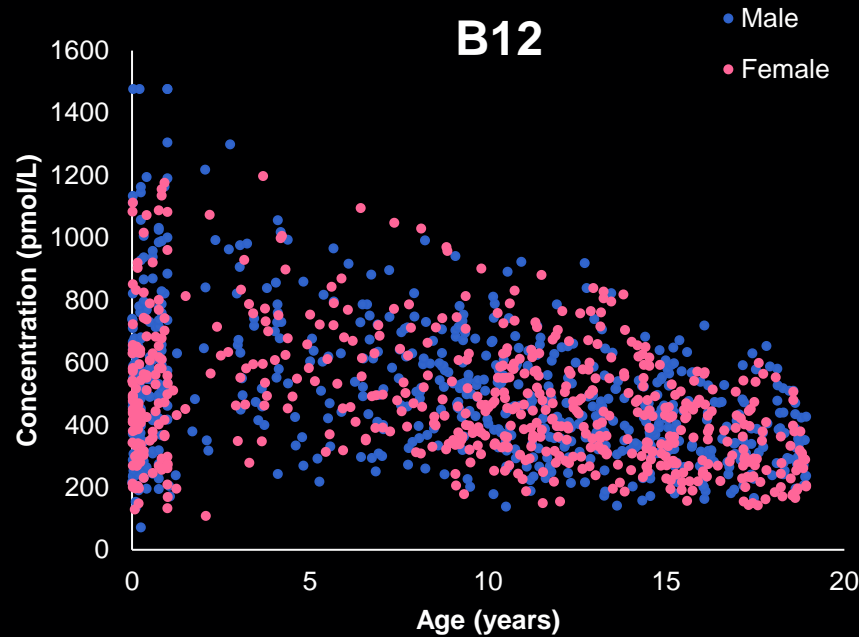
Insulin



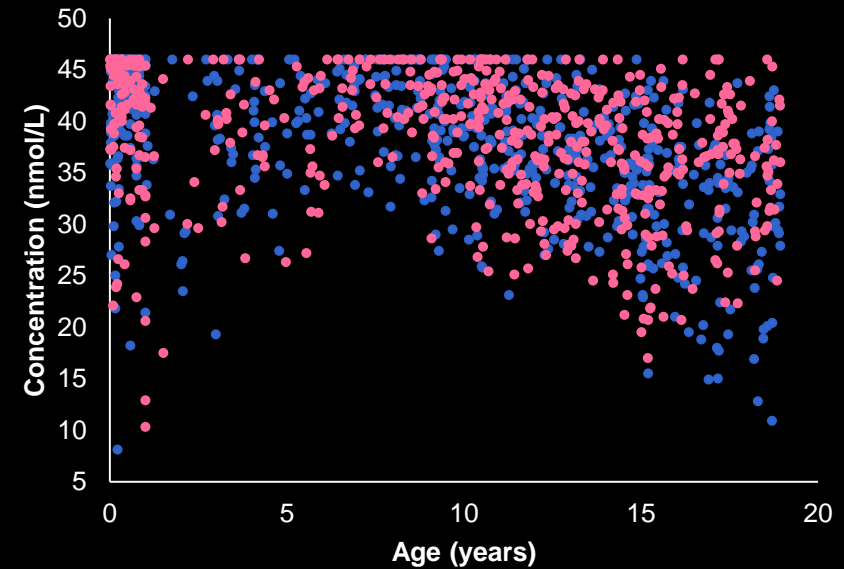
B-HCG



B12



Folate



CALIPER Reference Database

Reference Interval Transference & De Novo Establishment

Abbott



Roche



Siemens



Ortho



Beckman



CALIPER Reference Database

(CALIPER data widely published >50 publications)

- I. Biochemical Markers (*Chemistry, Proteins, Enzymes*)
 - *Colantonio et al. Clinical Chemistry 2012*

- II. Endocrine and Fertility Markers
 - *Bailey et al. Clin Chem 2013*
 - *Konforte et al. Clin Chem 2013*

- III. Vitamins and Cancer Markers
 - *Raizman et al. Clin Chem 2014*
 - *Bevilacqua et al. Clin Chem 2014*

- IV. Testosterone Indices, Metabolic, Specialized Biochemical Markers
 - *Raizman et al. Clin Chem Lab Med 2015*
 - *Teodoro-Morrison Clin Biochem 2015*
 - *Kelly et al. Clin Chim Acta 2015*

CALIPER Web & Mobile eApps

*To stay updated, download the
CALIPER mobile/web applications
and visit the website!*

www.caliperdatabase.org

www.caliperproject.org



CALIPER Database

www.caliperdatabase.org

New Mobile & Web Apps

Old Apps: >70 Biomarkers
New Apps: >180 Biomarkers

*Full Tables of Age- and Gender-Specific
Reference Intervals*



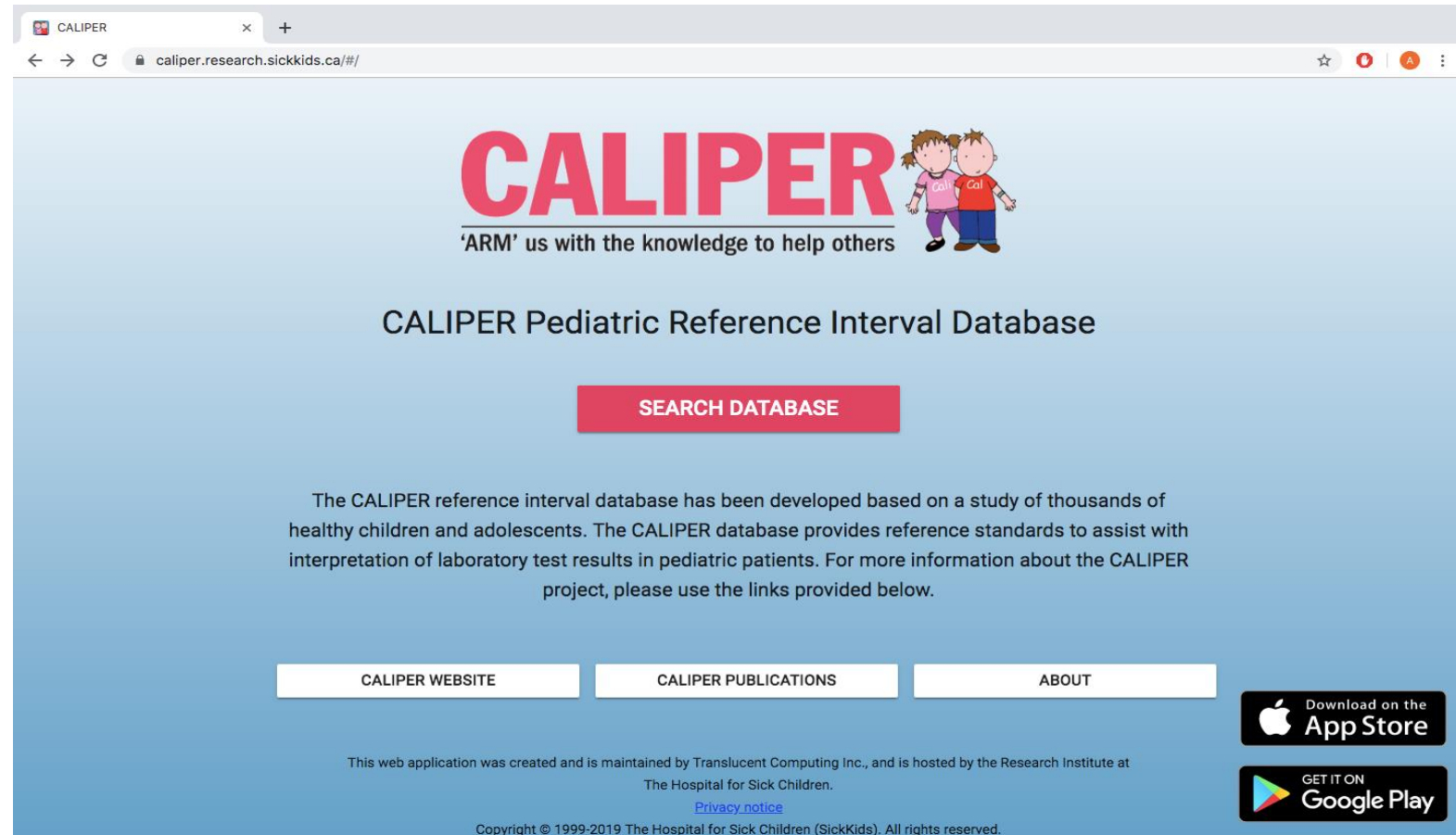
CALIPER Mobile App
(Available on Apple Store & Google Play)



CALIPER Web App

www.caliperdatabase.org

The CALIPER Web App has been developed for laboratory specialists, paediatricians, family physicians, other healthcare workers

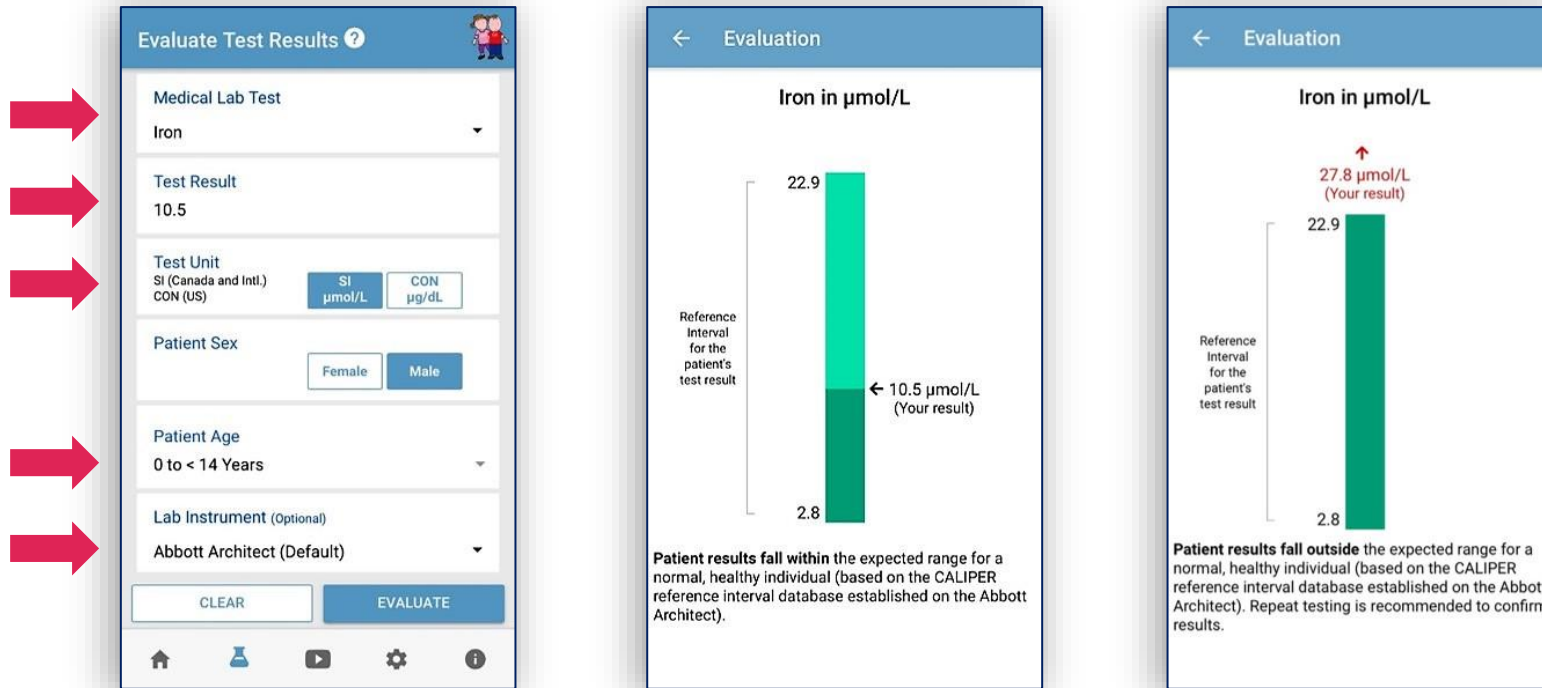


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A user friendly and easy tool to view latest reference value database developed based on thousands of healthy and ethnically diverse children and adolescents.

CALIPER Mobile App

Available on Apple Store and Google Play



Targeted to community pediatricians and healthcare workers to facilitate easy access to CALIPER database

CALIPER Objectives 2020-2021

I.

To expand CALIPER database to include new biomarkers.

II.

To expand CALIPER database to include new analytical platforms.

III.

To complete studies on continuous reference interval establishment.

IV.

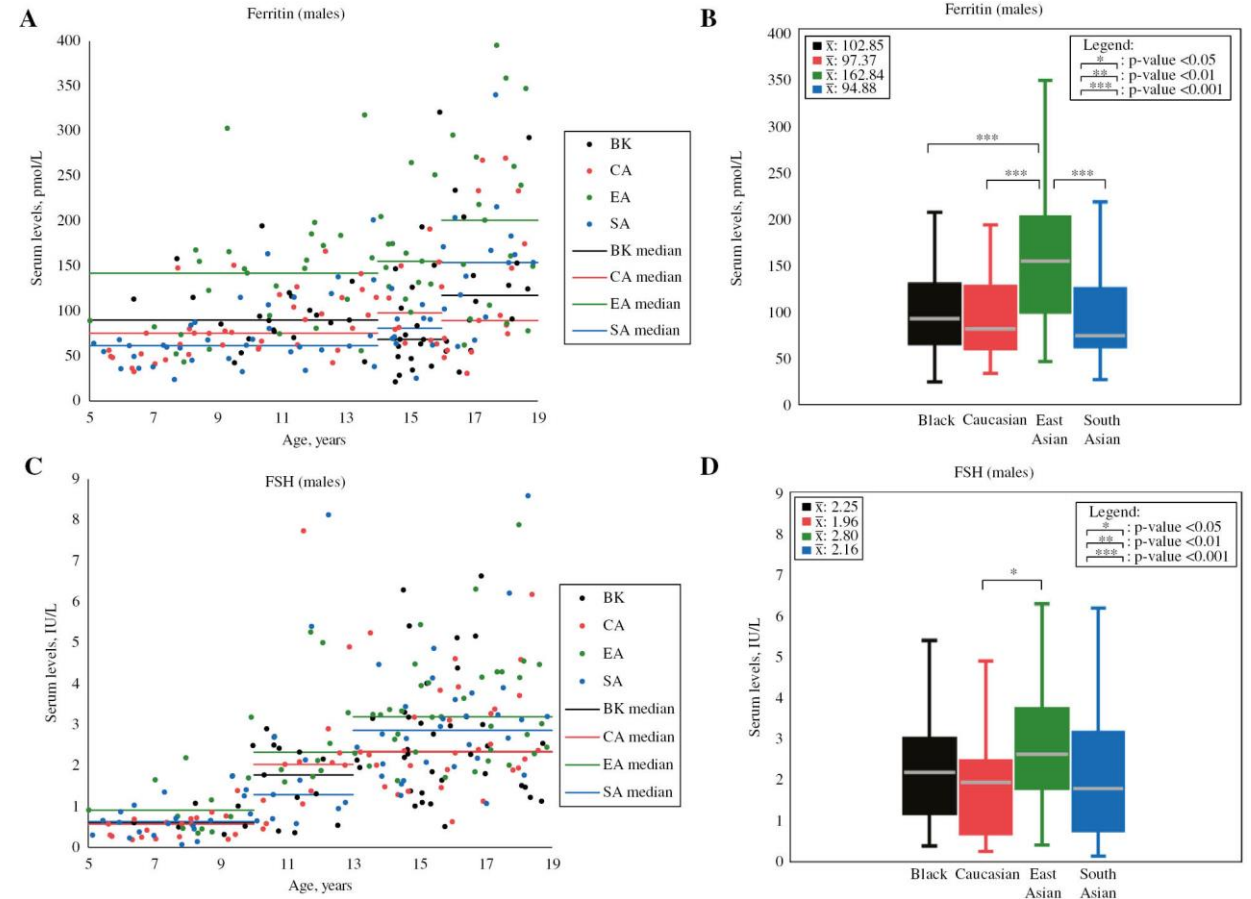
To complete studies on examining covariates such as ethnicity and BMI.

CALIPER Substudies

Published Studies:

Influence of ethnicity on biochemical markers of health and disease in the CALIPER cohort of healthy children and adolescents

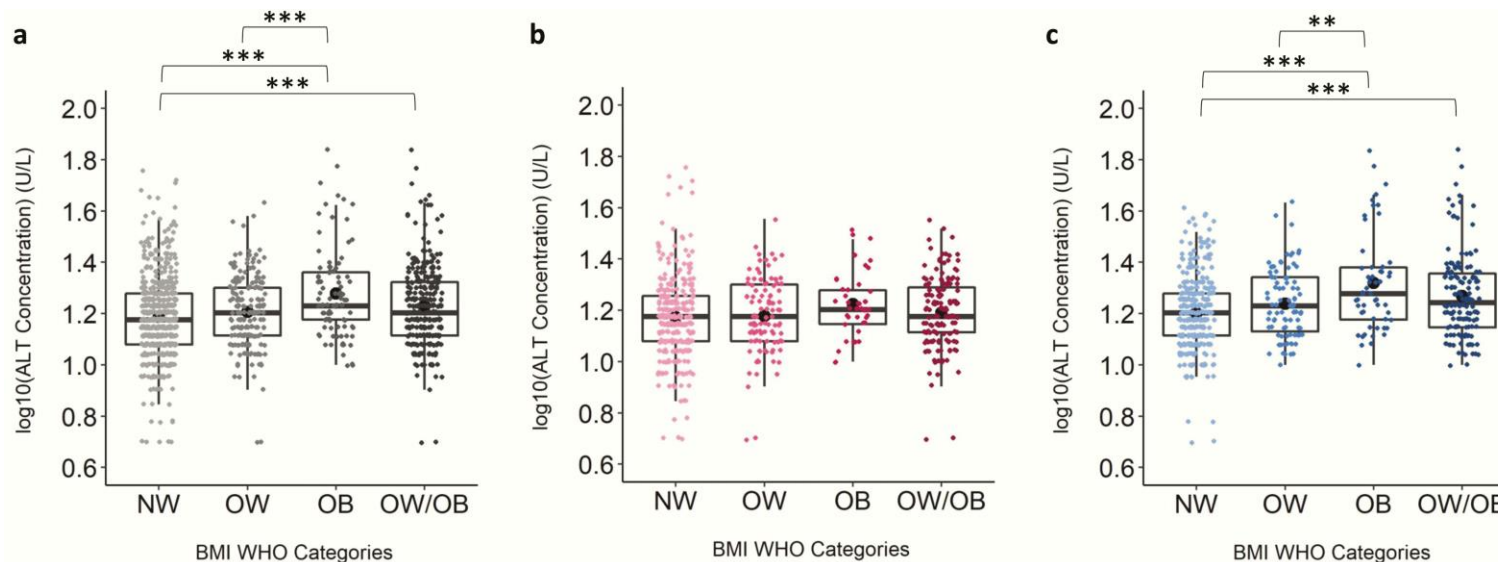
Tahmasebi H, et al. *Clin Chem Lab Med.* 2020;58(4):605-617.



Scatterplots and boxplots of male ferritin and FSH concentrations partitioned by ethnicity.

CALIPER Substudies

Marked Influence of Adiposity on Laboratory Biomarkers in a Healthy Cohort of Children and Adolescents. Higgins V, et al. *J Clin Endocrinol Metab.* 2020;105(4):e1781-e1797



Scatter boxplot of log(alanine aminotransferase [ALT]) concentration in normal weight (NW), overweight (OW), obese (OB), and overweight and obese combined (OW/OB) groups.

Ped Ref Intervals for New Biomarkers

Published Studies:

Establishment of RIs for hematology parameters on the Beckman DxH 900 & 520

- Tahmasebi H, et al. CALIPER Hematology Reference Standards (I). *Am J Clin Pathol.* 2020
- Higgins V, et al. CALIPER Hematology Reference Standards (II) . *Am J Clin Pathol.* 2020

Establishment of RIs for urea creatinine ratio on the Abbott Architect

- Bohn MK, et al. CALIPER paediatric reference intervals for the urea creatinine ratio in healthy children & adolescents. *Clin Biochem.* 2020;76:31-34.

In Progress Studies:

- Establishment of RIs for **hematology parameters** on the Sysmex-XN3000 (*publication under review*)
- Establishment of RIs for **trace elements** using in collaboration with Hamilton Health Sciences (*data analysis in progress*)
- Establishment of RIs for **POCT parameters** on the Radiometer ABL90 (*manuscript in preparation*)

Ped Ref Intervals for New Platforms

Published Studies:

Establishment of RIs for 17 immunoassays in the Roche cobas platform

- Bohn MK, et al. *Clin Chem Lab Med.* 2019;57(12):1968-1979.

Establishment of RIs for chemistry parameters on the Siemens ADVIA and Dimension EXL platform

- Tahmasebi H, et al. *Clin Chim Acta.* 2019;490:88-97.

In Progress Studies:

- Establishment of RIs for chemistry and immunoassay parameters on the **Siemens Atellica** (*manuscript in preparation*)
- Verification of RIs established on the Abbott ARCHITECT on the **Abbott Alinity** platform (*data analysis in progress*)
- Establishment of RIs for special chemistry parameters on the **DiaSorin Liason** platform (*data analysis in progress*)
- Establishment of RIs for hematology parameters on the **Mindray Hematology** platform (*study in planning stages*)

Continuous Reference Intervals

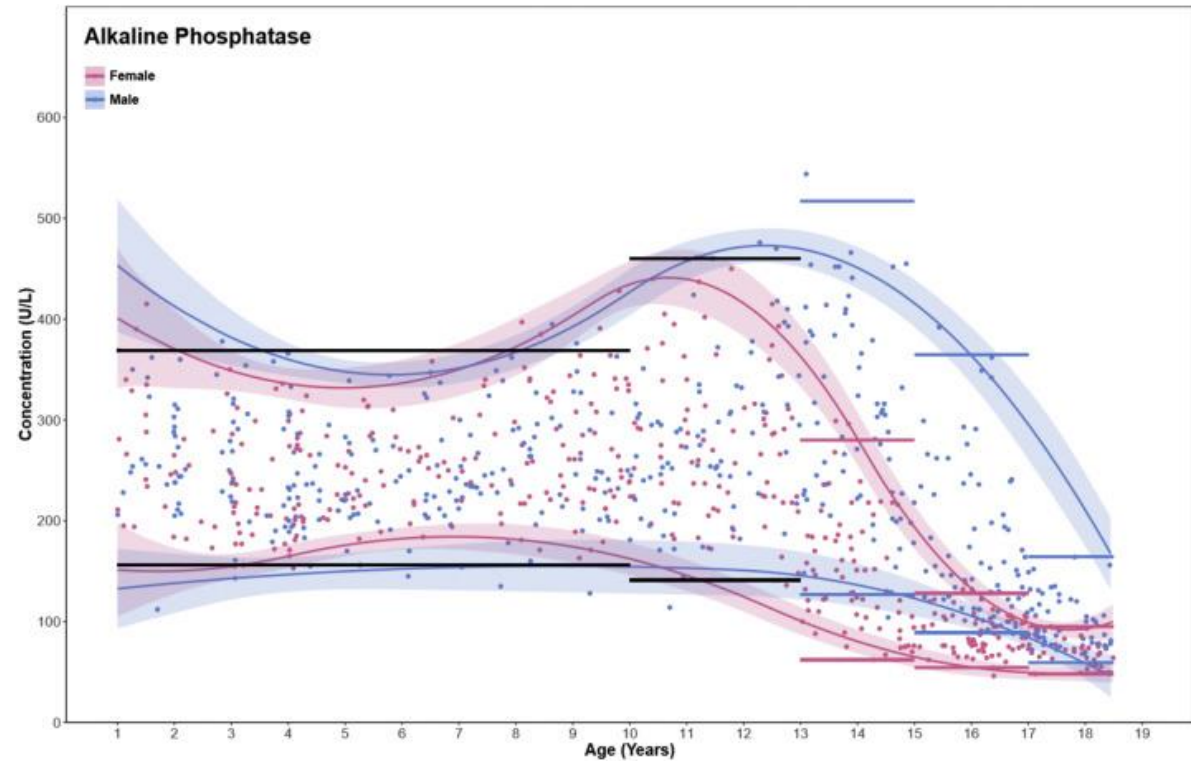
Published Studies:

Establishment of continuous RIs for 38 biochemical markers

- Asgari S, et al. *Clin Biochem.* 2019;73:82-89.

In Progress Studies:

- Establishment of continuous RIs for immunoassay and hematology parameters (*data analysis in progress*)



CALIPER Objectives: 2020-2021

I.

To continue to expand the CALIPER database to novel parameters and platforms.

II.

To establish trimester-specific RIs for pregnant women as part of CALIPER Mother & Child Study.

III.

To focus on recruitment of younger children to address previous study limitation.

IV.

To complete serological studies for SARS-CoV-2 in the CALIPER population.

You and your child can help improve the care of children with medical concerns at SickKids by participating in this study!

CALIPER

'ARM' us with the knowledge to help others



Why is this study important?
CALIPER is a community health project to improve the healthcare of young children at SickKids and other children's hospitals across Canada.

Who can participate?
We are looking for healthy children under 5 years of age to participate in CALIPER with their family's support. However, any child from birth to 18 can take part.

What does participation involve?
FOR YOU:
• Fill out a short questionnaire about your child's health
FOR YOUR CHILD:
• Height, weight and waist measurements
• Small blood donation (less than one tablespoon)

How will I benefit?
Participants will receive:
• CALIPER teddy bear or t-shirt
• \$10 honorarium

Want to learn more or have your child participate?



CONTACT US
Project Coordinator: Alexandra Hall
alexandra.hall@sickkids.ca
416-813-7654 Ext. 202673 | www.calliperproject.org
Version Date: June 18, 2020

You can help improve medical assessment of maternal health in pregnant women by participating in this study!

MOTHER & CHILD HEALTH INITIATIVE

A healthy start to a baby's life begins with a healthy pregnancy

What is this initiative?
The Mother and Child Health Initiative was developed to improve healthcare during and after pregnancy for both mother and child.

Who can participate?
Pregnant women aged 18 to 40 years. Participate at each trimester and up to 3 months postpartum and receive remuneration each time!

What does participation require?
• Completion of a consent form and questionnaire
• Height and weight measurements
• A small blood donation

How will I benefit?
• Blood test results, upon request
• \$20 honorarium
• Mother & Child gift basket

Interested in learning more or participating?



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Canadian Institutes of Health Research

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Version Date: June 18, 2020

CALIPER – Ongoing Studies

Addressing Remaining Gaps in Available Laboratory Tests

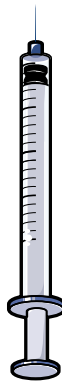
- Despite the richness of the CALIPER database, few evidence gaps continue to exist for specialized parameters in the pediatric population

Hematology



- Establishment of pediatric RIs for the **complete blood count** on multiple analytical platforms (*Sysmex, Beckman, Mindray*)

POCT Parameters



- Establishment of pediatric RIs for **critical care parameters** on POCT instruments (*Radiometer, NovaStatStrip*)

Trace Elements



- Establishment of pediatric RIs for **trace elements** (whole blood & plasma) using ICP-MS

Immune Studies



- Establishment of pediatric RIs for **cytokines** and **autoimmune markers**

Acknowledgments – CALIPER Team

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