Clinical Application of Metabolomics in Early Colorectal Cancer Detection

SYNEVO CLINICAL RESEARCH SYMPOSIUM, November 17th, 2017

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Head of Research in Universal DX
“Liquid biopsy coming of age”

- Invasive
- Time consuming
- Cannot be used for screening
- Profile restricted to biopsied cells
- Difficult to obtain
- Hard to use for disease monitoring

- Non-invasive
- Easily obtained
- Full profile of pathological state of the person
- Fast
- Good for screening
- Good for monitoring
Potential biomarkers in blood

Circulating tumour cells

miRNA

Monocytes

Proteins, Peptides

Tumour educated platelets

ctDNA

Metabolites

Lipids
Metabolites and lipids-distinct blood markers with biological function related to Cancer

Overview*

Comments

- Small <700 Da endogenous molecules
- Most markers have proven biological function in:
  - Carcinogenesis
  - Cell cycle regulation
  - Immunological response
  - Inflammatory development
  - Cell energy balance

*Source: http://www.genome.jp/
Advantages of metabolomics

Easily multiplexed and scalable

Low cost

Small quantity of blood needed

Accurately quantifiable

Early detection

Direct reflection of functional status of the organism

Tissue specific alterations = platform for other cancers

Expandable from detection to monitoring

High potential for clinical use

Source: http://metabolomics.ucdavis.edu/core-services/metabolites
Universal DX (UDX) is a startup with the mission to detect cancer early

Our Mission
UDX is a diagnostic medical device startup with the mission to research cancer and develop and commercialize blood tests for the early detection of cancer.

Metabolomics
Cancer initiation and progression changes the metabolism of human body, which manifests itself through the changing levels of small molecules (<600 Da), lipids and metabolites. UDX has identified and quantified a proprietary panel of biomarkers that allows to differentiate cancer and adenoma patients from controls.

Bioinformatics
UDX has a strong bioinformatics background for complex data combining analytical, biological pathway and meta-data analysis for selection and characterization of relevant markers as well as developing prediction algorithms.
Colorectal cancer is a global challenge

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>3</td>
<td>134K</td>
<td>55K</td>
</tr>
<tr>
<td>EU</td>
<td>3</td>
<td>345K</td>
<td>152K</td>
</tr>
<tr>
<td>China</td>
<td>4</td>
<td>253K</td>
<td>139K</td>
</tr>
</tbody>
</table>

Source: Universal DX, cancer.org, American Cancer Society, Chin J Cancer Res 2015, GLOBCAN
Early detection of colorectal cancer saves lives

Adenomas: 10 out of 10 survive 5 years

CRC stages I/II: 9 out of 10 survive 5 years

CRC stage IV: 1 out of 10 survive 5 years

Adenoma detection prevents cancer

Source: SEER 18 2004-2010
Approx. 75% of CRCs are sporadic and originate from adenomatous colon polyps.
UDX’s CRC test

High accuracy

Adenoma detection

Simple to use blood test

Low cost

Platform for other cancers

UDX test prevents colorectal cancer

Source: Universal Diagnostics
UDX test with high sensitivity and specificity

Global performance

- Sensitivity CRC: 87%
- Sensitivity Polyps: 83%
- Specificity: 83%

Stage specific performance

- Stage 1: 85%
- Stage 2: 82%
- Stage 3: 94%
- Stage 4: 89%
- Overall: 87%

AUC = 92% on 30-marker panel

682 caucasian retrospective samples, balanced data set (age, gender, condition)

Source: Universal Diagnostics
## Detailed overview of 30 panel markers

### Overview markers – amino acids

<table>
<thead>
<tr>
<th>Marker</th>
<th>Pathway</th>
<th>Sub Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amino Acid</td>
<td>Lysine Metabolism</td>
</tr>
<tr>
<td>2</td>
<td>Amino Acid</td>
<td>Histidine Metabolism</td>
</tr>
<tr>
<td>3</td>
<td>Amino Acid</td>
<td>Urea cycle; Arginine and Proline Metabolism</td>
</tr>
<tr>
<td>4</td>
<td>Amino Acid</td>
<td>Urea cycle; Arginine and Proline Metabolism</td>
</tr>
<tr>
<td>5</td>
<td>Amino Acid</td>
<td>Methionine, Cysteine, SAM and Taurine Metabolism</td>
</tr>
<tr>
<td>6</td>
<td>Amino Acid</td>
<td>Polyamine Metabolism</td>
</tr>
<tr>
<td>7</td>
<td>Amino Acid</td>
<td>Alanine and Aspartate Metabolism</td>
</tr>
<tr>
<td>8</td>
<td>Amino Acid</td>
<td>Tryptophan Metabolism</td>
</tr>
<tr>
<td>9</td>
<td>Amino Acid</td>
<td>Phenylalanine and Tyrosine Metabolism</td>
</tr>
<tr>
<td>10</td>
<td>Amino Acid</td>
<td>Glutamate Metabolism</td>
</tr>
<tr>
<td>11</td>
<td>Amino Acid</td>
<td>Lysine Metabolism</td>
</tr>
<tr>
<td>12</td>
<td>Amino Acid</td>
<td>Glycine, Serine and Threonine Metabolism</td>
</tr>
<tr>
<td>13</td>
<td>Amino Acid</td>
<td>Tryptophan Metabolism</td>
</tr>
<tr>
<td>14</td>
<td>Amino Acid</td>
<td>Phenylalanine and Tyrosine Metabolism</td>
</tr>
<tr>
<td>15</td>
<td>Amino Acid</td>
<td>Methionine, Cysteine, SAM and Taurine Metabolism</td>
</tr>
<tr>
<td>16</td>
<td>Amino Acid</td>
<td>Lysine Metabolism</td>
</tr>
</tbody>
</table>

### Overview markers – lipids, others

<table>
<thead>
<tr>
<th>Marker</th>
<th>Pathway</th>
<th>Sub Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Cofactors and Vitamins</td>
<td>Nicotinate and Nicotinamide Metabolism</td>
</tr>
<tr>
<td>18</td>
<td>Lipid</td>
<td>Phospholipid Metabolism</td>
</tr>
<tr>
<td>19</td>
<td>Lipid</td>
<td>Phospholipid Metabolism</td>
</tr>
<tr>
<td>20</td>
<td>Lipid</td>
<td>Phospholipid Metabolism</td>
</tr>
<tr>
<td>21</td>
<td>Lipid</td>
<td>Fatty Acid, Dicarboxylate</td>
</tr>
<tr>
<td>22</td>
<td>Lipid</td>
<td>Fatty Acid Metabolism (also BCAA Metabolism)</td>
</tr>
<tr>
<td>23</td>
<td>Lipid</td>
<td>Fatty Acid, Dicarboxylate</td>
</tr>
<tr>
<td>24</td>
<td>Lipid</td>
<td>Fatty Acid, Dicarboxylate</td>
</tr>
<tr>
<td>25</td>
<td>Lipid</td>
<td>Polyunsaturated Fatty Acid (n3 and n6)</td>
</tr>
<tr>
<td>26</td>
<td>Lipid</td>
<td>Phospholipid Metabolism</td>
</tr>
<tr>
<td>27</td>
<td>Lipid</td>
<td>Fatty Acid Metabolism (Acyl Carnitine)</td>
</tr>
<tr>
<td>28</td>
<td>Nucleotide</td>
<td>Purine Metabolism, Adenine containing</td>
</tr>
<tr>
<td>29</td>
<td>Nucleotide</td>
<td>Pyrimidine Metabolism, Cytidine containing</td>
</tr>
<tr>
<td>30</td>
<td>Xenobiotics</td>
<td>Benzoate Metabolism</td>
</tr>
</tbody>
</table>

Diverse types of molecules, all small metabolites (<600 Daltons, Lipids <900 Dalton) - Classes are amino acids, nucleotides, lipids
**Phospholipids as major players in UDX panel**

De novo lipogenesis - highly regulated metabolic pathway

**In cancer** de novo fatty acid synthesis is necessary to maintain a constant supply of lipids and lipid precursors to fuel membrane production and lipid-based posttranslational modification of proteins in a highly proliferating cell population.

Increase in saturated phospholipids (PLs):
- alters signal transduction,
- protects cancer cells from oxidative damage such as lipid peroxidation and
- potentially inhibits the uptake of chemotherapeutic drugs
- lipids can also be broken down into bioactive lipid mediators, which regulate a variety of carcinogenic processes:
  - including cell growth
  - cell migration and
  - metastasis formation

Aim of the latest study

• Use clinical data to better characterize the patients

• Verify whether metabolomic technology can be successfully used to distinguish patients with advanced adenomatous polyps with good accuracy

• Verify whether the technology could be further used for sub-categorization of adenoma patients according to their pathological severity
Study population
Sample cohort from Hospital Clínic de Barcelona

### Classes

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>NAA</th>
<th>CNTRL</th>
<th>Hyperplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>39</td>
<td>45</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>21</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>24</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td>58.21 (±5.3)</td>
<td>60.98 (±5.8)</td>
<td>60.57 (±5.5)</td>
<td>57.75 (±5.7)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td> </td>
<td>26.1 (±3.7)</td>
<td>26.13 (±3.9)</td>
<td>26.14 (±4.5)</td>
<td>25.52 (±2.9)</td>
</tr>
</tbody>
</table>

AA: Advanced adenoma; NAA: Non-advanced adenoma; CNTRL: control; Hyperplastic (polyps): Benign condition

Prospective serum samples were collected from 131 participants in a colon cancer screening program
Promising results based on metabolomics

PCA and ROC curve analysis showing good separation power for advanced adenoma and control as well as potential for adenoma sub-classification

Figure 1. Principal components analysis (PCA) comparing a) AA vs. Control, b) AA vs. ControlHyperplasticNAA, c) AA vs. NAA.

Figure 3. ROC Curve for the best marker to discriminate between a) AA vs. Control and b) AA vs. ControlHyperplasticNAA.
Promising results based on metabolomics

<table>
<thead>
<tr>
<th>Problem</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced adenoma vs Control</td>
<td>87%</td>
<td>73%</td>
</tr>
<tr>
<td>Advanced adenoma vs extended Control set including:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- hyperplastic polyp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- non-advanced adenoma</td>
<td>81%</td>
<td>70%</td>
</tr>
<tr>
<td>Advanced adenoma vs Non-Advanced adenoma</td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Further studies under way

Source: Universal Diagnostics
Next steps: Clear focus on CRC test towards commercialization

- Clinical validation
  - Finish research and validate UDX test in a large scale study
  - Publish results in peer-reviewed magazines

- Patent
  - Ensure successful filing of biomarker panel and sample preparation patent
  - Push additional IP protection

- Quality system
  - Apply and successfully pass audit for ISO 13485 and US equivalent QMS

- Regulatory approvals
  - For Europe, ensure CE mark approval and IVD producer registration
  - For US, build CLIA lab and go to market with lab-developed test and move towards PMA

- Sales
  - Close distribution partnerships in Europe, US, and potential China
# UDX collaborates with global institutions

<table>
<thead>
<tr>
<th>Research &amp; Development</th>
<th>Clinical validation</th>
<th>Operations</th>
</tr>
</thead>
</table>
| Imperial College London | • Marker research  
• Data analysis  
• Publications | • Prospective collection  
• ES, BE, NL, UK, US  
• Key equipment and material suppliers  
• New equip./maint. |
| UPC | • Marker research bioinformatics  
• Publications | • IP strategy  
• Patents |
| imus | • Algorithm development  
• Publications | • QMS  
• Regulatory |
| AB SCIEX | • Finance | • Singularity University |
| HAMILTON | | • Legal |
| SIGMA-ALDRICH | | |
| Fisher Scientific | | |
| Waters | | |
Key opinion leaders support UDX

Dr. Toni Castells
- Clinic Hospital, Barcelona, Spain
- Medical Director
- Head of CRC Screening Program

Dr. Uri Ladabaum
- Stanford University, Palo Alto, USA
- Head of Colorectal Cancer Screening Program

Dr. Josep Tabernero
- Vall d’Hebron, Barcelona, Spain
- Director of the Institute of Oncology

Prof. Uwe Bicker
- German Cancer Center, Heidelberg, Germany
- Honorary Senator
- Member of various Boards of Directors (e.g. Sanofi)

Prof. Jeremy Nicholson
- Imperial College, London, UK
- Head of Department Surgery & Cancer
- Founding director Phenome Center UK

Source: Universal Diagnostics
A great team ...

Management

Juan Founder & Chairman
MIT MBA

Marko Founder & CTO
MSc. Biotechnology

Christian COO
Insead MBA

Kristi Head of R&D
M.Sc Biochemistry

Rosa S. Research.
PhD Chemical Sciences

Ángela Researcher
PhD Chemistry

Rosa Researcher
PhD Chemistry Engineering

Patricia Researcher
M.Sc Advanced Biotechnology

Antonio Data Science
Manager M.Sc Computer Science

Candela Controller
B.Sc Business Administration

A great team ...

R&D / Biostatistics

Medical affairs

Alvaro Operat. Mgr.
MBA

Cristobal CP Manager
B.Sc Economics

Juan CP Manager
M.Sc Clinical Research
Biotechnology Monitoring & Trials

Paola Lab Director
PhD. Biotechnology

Puri Lab PM
M.Sc Quality & Environmental Management

Ana Lora Lab Techn.
M.Sc Food Processing

Carolina Lab Techn.
B.Sc Environmetal Sciences

Andrea Lab Techn.
CertHE Lab Technician

QMS

RA

Responsives

Source: Universal DX
Thank you for your attention!

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