PROTEOMICS IN CLINICAL PRACTICE-
BARRIERS TO ADOPTION

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NSW PATHOLOGY AT LIVERPOOL AND ROYAL PRINCE ALFRED HOSPITAL
TIME FOR A REALITY CHECK?
BARRIERS TO UPTAKE

• Complexity of Technology
• Cost and Reimbursement Rates
• Measurement Errors
• Throughput
• Clinical Utility
• Skill Base in Technology and Informatics
MS Systems

• Create ions from analyte proteins
• Separation based on charge and mass
• Detect ions and determine mass to charge
• Select ions of interest to give structural information (with or without fragmentation)
MS/MS means using two mass analyzers (combined in one instrument) to select an analyte (ion) from a mixture, then generate fragments from it to give structural information.
Technology Issues

- Top down/ bottom up
- Sample prep may be complex/manual/prolonged
- May require LC and/or other separation methods
- Detector choice-MS/MS-TOF MS-Ion trap (orbitrap) etc.
- Sensitivity requirements for high MW compounds
U.S. Proteomics Market By Product, USD Million, 2013 - 2024
COST COMPARISON MS VS IMMUNOASSAY
ASSUMPTIONS

- LCMS+ Autoprep $600K-life 5 years
- LCMS service contract $50K/pa
- LCMS reagents & column 90 cents per test
- LCMS labor SHS equivalent $120K pa
- I/A use current multiuse equipment- 50 cents per test
- I/A reagent say $4 /test
- I/A labor TO equivalent $60K pa

Fixed costs-QC/QAP/rent/ electricity equivalent
## Unit Test Costs - $

<table>
<thead>
<tr>
<th>Tests/day</th>
<th>MS</th>
<th>Immunoassay</th>
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<tbody>
<tr>
<td>50</td>
<td>29.60</td>
<td>11.50</td>
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<tr>
<td>100</td>
<td>15.10</td>
<td>7.50</td>
</tr>
<tr>
<td>200</td>
<td>7.85</td>
<td>6</td>
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MBS is Technology Agnostic

Quantitation in blood or urine of hormones and hormone binding proteins - ACTH, aldosterone, androstenedione, C-peptide, calcitonin, cortisol, DHEAS, 11-deoxycortisol, dihydrotestosterone, FSH, gastrin, glucagon, growth hormone, hydroxyprogesterone, insulin, LH, oestradiol, oestrone, progesterone, prolactin, PTH, renin, sex hormone binding globulin, somatomedin C (IGF-1), free or total testosterone, urine steroid fraction or fractions, vasoactive intestinal peptide. - 1 test

(Item is subject to rule 6)

(See para TN.1.4 of explanatory notes to this Category)

Fee: $30.50  Benefit: 75% = $22.90  85% = $25.95
MBS FUNDING OF NEW TESTING

- Application to MSAC
- Outcome evidence essential
  
  *Suitability to pathology testing questionable*

- Who funds application?
CLINICAL UTILITY

• Better analytical specificity

• Immunoassay \( V \) LC-MS

• LC-MS superior—or just different?

• Does either measure the sum of biologically active forms?
MEASUREMENT ERRORS

• Pre-analytical – poor reproducibility
• Standards
• QC & QA
• Database deficiencies
QA/QC REQUIREMENTS

- INDIVIDUAL PROTEIN STANDARDS
- HOMOGENEOUS
- STABLE
- CLINICALLY USEFUL PROTEINS
- VALIDATED

ACHIEVABLE?
QC/QA VALIDATION

- STANDARDISATION - the desirable level of traceability - the results are equivalent and traceable to a Primary Reference Material or Reference measurement Procedure

- HARMONISATION - results are equivalent and traceable to reference material or consensus approach and methodology
• Unique protein/peptide
• Protein Isoforms
• Degradation products
• Post translational modifications
• SNPs
An error rate of 5–20%, dependent upon the degree of difficulty for each EQA, currently exists amongst the four European laboratory schemes (see Annual Reports from CEQA, CF Network, EMQN and ERNDIM). While this may be an overestimation of the true error rates with diagnostic samples, it clearly highlights the fact that a significant number of laboratories are in urgent need of improving their procedures and the quality of their diagnostic analysis.
BUT

• Small number of labs doing same test
• 3000 genetic tests offered-how can that quality be assured??
• The complete Request- Test- Report Cycle or Collection-Analysis-Interpretation
• Informatics EQA
Quality Use of Pathology Program
APPLICATION FOR FUNDING

Summary

Organisation: RCPA Quality Assurance Programs Pty Ltd
Total Amount of Funding (Including GST) Sought:

Duration of Project (years/months): 12 months
Brief Summary of Application:

<table>
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<td>The development of a mass spectrometry technical quality assurance program for detecting human disease-associated proteins.</td>
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<tr>
<th>Short Description (max: 150 words)</th>
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<td>Funding is sought for the development of a mass spectrometry quality assurance program for proficiency testing in the new field of proteomic diagnostic analysis. Identifying abnormal proteins in response to genetic DNA variation, microbial infection, or as a further consequence of the underlying disease pathology, is key to understanding the disease process. This information is essential for clinicians when developing a treatment regime for patients. Critically, no quality assurance program exists to determine the ability of Australasian laboratories to accurately test for proteins diagnostically associated with disease. QUPP funding was previously obtained in 2013 for the development of somatic cancer modules for gene variant biomarker testing in genes associated with different cancers. The current proposal will build on</td>
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WHO IS GOING TO PERFORM AND INTERPRET PROTEOMICS TESTING?
Policy

Subject: Fellowship of the Faculty of Science (Pathology Informatics) RCPA
Approval Date: April 2018
Review Date: April 2021
Review By: Faculty of Science Committee
Number: 2/2018
Up-skilling of Pathologists

Proteomics in Chemical Pathology Curriculum

RCPA Introduction to Proteomics in Pathology-2017

Pathology Update-2018-Direct MS profiling of histological tissues-Zoltan Takats

Pathology Update-2019

- Success of Precision Pathology-Multi-omics Building Blocks -Daniel Chan
- Clinical Proteomics-Development of a Pathology Partnership-Multiple presenters

Proteomics in Pathology-2019
Cautious optimism
High Value-Low Volume Testing