Next-Gen Precision Diagnostics

INOVIQ (IIQ) is focused on developing diagnostics and exosome-based solutions for cancer and other diseases, aimed at earlier and more accurate detection to improve treatment options and patient outcomes. Its pipeline of promising, versatile next-generation blood-based test candidates span various stages of development. These candidates have multiple potential applications and commercial opportunities.

Data rendered for IIQ's most advanced asset, the SubB2M ligand (recombinant protein), shows unprecedented specificity and sensitivity in detecting ovarian and breast cancers across all stages. Combined with existing tests, SubB2M could represent a step change in both detection of early-stage cancer and monitoring of late-stage cancer.

Diversified Portfolio of Versatile Technology Platforms and Products

EXO-NET: innovative tool to capture exosomes for liquid biopsies – UQ collaboration underway. EXO-NET delivers an efficient, optimal process to capture exosomes from all major biofluids. Exosomes, which can be seen as cellular 'messages in a bottle', hold important information about the status of their parent cells (normal or malignant, healthy, or diseased), which can inform clinical decisions, treatment selection and patient management. EXO-NET could have many applications to address unmet needs.

A collaboration with the University of Queensland (UQ) is developing a novel multivariate index assay for early ovarian cancer detection – a high unmet need. The collaboration combines EXO-NET exosome capture and UQ's OCRF-7 ovarian cancer biomarkers.

SubB2M: strong data in ovarian, breast cancers support potential to supercharge current tests and monitor disease progression. This technology platform uses SubB2M, a proprietary, novel, highly selective ligand. SubB2M binds to Neu5Gc, a promising new pan-cancer marker found at elevated levels in many human cancers (and not in healthy cells). Compelling data has been rendered across all stages of ovarian and breast cancers. The technology could potentially significantly improve both detection of early-stage cancer (by reducing false negatives and false positives of existing single biomarker cancer tests: CA125, CA15.3) and monitoring for late-stage cancer.

BARD1: novel autoantibody technology for potential earlier cancer detection. IIQ's proprietary autoantibody test to aberrant BARD1 proteins (associated with cancer formation and poor prognosis) represents another promising basis of diagnostic assay for early detection of cancer. Potential applications include lung, breast, and ovarian cancers.

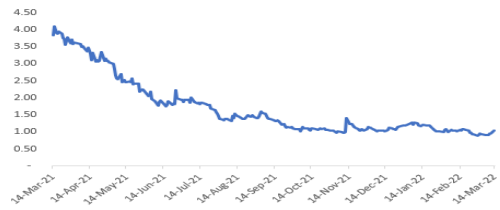
INOVIQ is a development -stage clinical diagnostics company focused on novel biomarker-based assays and exosome-based solutions for early detection of cancers and other diseases. Its portfolio includes three novel liquid biopsy technologies for monitoring and earlier detection of ovarian and breast cancers. Previously commercialised products include: the hTERT test, an ICC (immunocytochemical) test for use as an adjunct to urine cytology testing for bladder cancer, and RUO EXO-NET, a pan-exosome capture tool used in research settings.

Stock	IIQ.ASX
Price	A$0.54
Market cap	A$49m
Valuation	A$2.11

Company data	
Net cash (as at 30 June 2022)	$15.3m
Shares on issue	92.0m
Code ASX	IIQ

Share price catalysts – 2HCY22
SubB2M clinical testing– BC and OC monitoring
Exosome-based OC test development progress

IIQ share price (A$)



Source: FactSet.

Chris Kallos, CFA
chris.kallos@mstaccess.com.au

Valuation

We value IIQ at A$195m or A$2.11 per share (undiluted), using a risk-adjusted net present value (rNPV) method to discount future cash flows through to 2043, consistent with the expiry life of patent families. Key risks to our valuation: demonstrating efficacy, establishing clinical utility, meeting regulatory requirements.

Financials

Exhibit 1: Summary financials

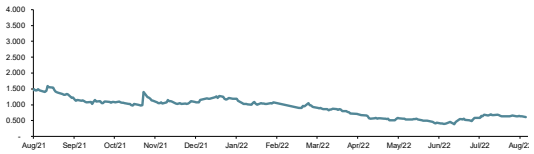
INOVIQ LTD IIQ — **IIQ-AU**

Year end 30 June, AUD unless otherwise noted

MARKET DATA

Price	**$**	**0.57**
52 week high / low	$	0.83-3.7
Valuation	**$**	**2.11**
Market capitalisation	$m	52.5
Shares on issue (basic)	**m**	92.0
Options / rights	m	9.3
Other equity	m	0.0
Shares on issue (diluted)	**m**	**101.4**

12-MONTH SHARE PRICE PERFORMANCE (A$)



INVESTMENT FUNDAMENTALS		FY20A	FY21A	FY22E	FY23E	FY24E
Reported NPAT	$m	(3.3)	(11.2)	(9.2)	(10.4)	(9.8)
Underlying NPAT	**$m**	**(3.3)**	**(11.2)**	**(9.2)**	**(10.4)**	**(9.8)**
Reported EPS (diluted)	¢	(0.2)	(14.4)	(10.0)	(11.3)	(10.6)
Underlying EPS (diluted)	**¢**	**(0.2)**	**(14.4)**	**(10.0)**	**(11.3)**	**(10.6)**
Growth	%		5947.8%	-30.9%	13.1%	-5.8%
Underlying PER	x	**nm**	**nm**	**nm**	**nm**	**nm**
Operating cash flow per share	¢	(0.2)	(6.8)	(9.1)	(10.4)	(9.8)
Free cash flow per share	¢	(0.2)	(3.0)	(9.1)	(10.4)	(9.8)
Price to free cash flow per share	**x**	**nm**	**nm**	**nm**	**nm**	**nm**
FCF Yield	%	nm	nm	nm	nm	nm
Dividend	¢	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Payout	%	0.0%	0.0%	0.0%	0.0%	0.0%
Yield	**%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**
Franking	%	0.0%	0.0%	0.0%	0.0%	0.0%
Enterprise value	**$m**	**45.1**	**48.7**	**40.0**	**49.6**	**58.6**
EV/EBITDA	x	(13.9)	(3.7)	(4.8)	(5.2)	(6.5)
EV/EBIT	x	(13.9)	(3.5)	(4.4)	(4.8)	(6.0)
Price to book (NAV)	x	1.7	1.8	1.4	1.9	2.9
Price to NTA	x	1.7	18.0	4.0	15.9	(9.1)

KEY RATIOS		FY20A	FY21A	FY22E	FY23E	FY24E
EBITDA margin	%	nm	nm	nm	nm	nm
EBIT margin	%	nm	nm	nm	nm	nm
NPAT margin	%	nm	nm	nm	nm	nm
ROE	%	nm	nm	nm	nm	nm
ROA	%	nm	nm	nm	nm	nm
Net tangible assets per share	$	0.3	0.0	0.1	0.0	(0.1)
Book value per share	$	0.3	0.3	0.4	0.3	0.2
Net debt/(cash)	$m	(7.3)	(3.7)	(12.4)	(2.8)	6.2
Interest cover/ (EBIT/net interest)	x	nm	nm	nm	nm	nm
Gearing (net debt/EBITDA)	x	nm	nm	nm	nm	(0.7)
Leverage (net debt/(net debt + equity))	x	nm	nm	nm	nm	0.3

DUPONT ANALYSIS		FY20A	FY21A	FY22E	FY23E	FY24E
Net Profit Margin	%	nm	nm	nm	nm	nm
Asset Turnover	x	-	0.0	0.0	0.1	0.5
Return on Assets	%	nm	nm	nm	nm	nm
Leverage	x	1.1	1.2	1.1	1.2	1.2
Return on Equity	%	nm	nm	nm	nm	nm

KEY PERFORMANCE INDICATORS	FY20A	FY21A	FY22E	FY23E	FY24E
SubB2M				0.2	3.8
SubB2M				0.1	3.5
EXO-NET Research Use Only				1.1	4.5
EXO-NET DX (Clinical)				0.0	0.0
hTert			0.5	0.3	0.3

HALF YEARLY DATA		2H21	1H22	2H22	1H23	2H23
Product revenue	$m	0.3	0.1	0.2	0.1	0.1
Operating expenses	$m	(11.9)	(4.4)	(6.6)	(6.1)	(6.1)
EBITDA	$m	(9.9)	(3.3)	(5.1)	(5.2)	(5.2)
EBIT	$m	(10.8)	(3.3)	(5.9)	(5.2)	(5.2)
PBT	$m	(10.8)	(3.3)	(5.9)	(5.2)	(5.2)
Reported NPAT	$m	(7.9)	(2.7)	(6.5)	(5.2)	(5.2)

PROFIT AND LOSS		FY20A	FY21A	FY22E	FY23E	FY24E
Product revenue	**$m**	**0.0**	**0.5**	**0.3**	**1.7**	**12.2**
income	$m	**0.6**	**1.0**	**1.5**	**1.4**	**2.2**
Operating expenses	$m	(3.9)	(15.5)	(11.0)	(12.1)	(12.3)
EBITDA	**$m**	**(3.3)**	**(13.1)**	**(8.3)**	**(9.6)**	**(9.0)**
Depreciation & Amortisation	$m	0.0	(0.9)	(0.8)	(0.8)	(0.8)
EBIT	**$m**	**(3.3)**	**(14.0)**	**(9.2)**	**(10.4)**	**(9.8)**
Interest expense	$m	0.0	(0.1)	(0.1)	(0.1)	(0.1)
Pretax Profit	$m	(3.3)	(14.0)	(9.2)	(10.4)	(9.8)
Tax expense	$m	0.0	2.9	0.0	0.0	0.0
Reported NPAT	**$m**	**(3.3)**	**(11.2)**	**(9.2)**	**(10.4)**	**(9.8)**
Weighted average diluted shares	m	1,363.4	77.3	92.0	92.0	92.0

GROWTH PROFILE		FY20A	FY21A	FY22E	FY23E	FY24E
Revenue	%	nm	nm	(40.0)	5.0	5.0
EBITDA	%	89.5	303.1	(36.5)	14.8	(5.8)
EBIT	%	89.5	331.1	(34.6)	13.1	(5.8)
Reported NPAT	%	89.5	242.7	(17.7)	13.1	(5.8)

BALANCE SHEET		FY20A	FY21A	FY22E	FY23E	FY24E
Cash	$m	7.3	5.0	13.7	4.1	(4.9)
Receivables	$m	0.0	0.2	0.2	0.2	0.2
Other	$m	0.0	0.4	0.4	0.4	0.4
Current assets	**$m**	**7.4**	**5.6**	**14.3**	**4.8**	**(4.3)**
PPE	$m	0.0	0.6	0.6	0.6	0.6
Intangible assets	$m	0.0	15.1	14.4	13.6	13.0
Goodwill	$m	0.0	11.0	11.0	11.0	11.0
Other	$m	0.0	1.1	2.5	2.4	2.4
Non current assets	**$m**	**0.0**	**27.9**	**28.5**	**27.7**	**26.9**
Total assets	**$m**	**7.4**	**33.5**	**42.8**	**32.4**	**22.7**
Trade and other payables	$m	0.8	0.8	0.8	0.8	0.8
Lease liabilities	$m	0.0	0.3	0.3	0.3	0.3
Other	$m	0.1	0.4	0.4	0.4	0.4
Current liabilities	**$m**	**0.9**	**1.5**	**1.5**	**1.5**	**1.5**
Lease liabilities	$m	0.0	0.9	0.9	0.9	0.9
Other liability	$m	0.0	2.1	2.1	2.1	2.1
Non current liabilities	**$m**	**0.0**	**3.0**	**3.0**	**3.0**	**3.0**
Total liabilities	**$m**	**0.9**	**4.5**	**4.5**	**4.5**	**4.5**
Net assets	**$m**	**6.5**	**29.1**	**38.3**	**28.0**	**18.2**
Share capital	$m	19.3	51.8	70.3	70.3	70.3
Retained earnings	$m	(12.8)	(24.0)	(33.1)	(43.5)	(53.3)
Other	$m	0.0	1.2	1.2	1.2	1.2
Total equity	**$m**	**6.5**	**29.1**	**38.3**	**28.0**	**18.2**

CASH FLOW		FY20A	FY21A	FY22E	FY23E	FY24E
Net loss for period	**$m**	**(3.3)**	**(11.2)**	**(9.2)**	**(10.4)**	**(9.8)**
Depreciation & Amortisation	$m	0.0	(0.9)	(0.8)	(0.8)	(0.8)
Changes in working capital	$m	0.4	(0.4)	0.0	0.0	0.0
Other	$m	0.3	7.2	1.7	1.6	1.5
Operating cash flow	**$m**	**(2.5)**	**(5.3)**	**(8.3)**	**(9.6)**	**(9.0)**
Payments for PPE	$m	0.0	(0.8)	(0.1)	0.0	0.0
Other	$m	0.0	3.8	0.0	0.0	0.0
Investing cash flow	**$m**	**0.0**	**3.0**	**(0.1)**	**0.0**	**0.0**
Equity	$m	2.5	0.3	18.5	0.0	0.0
Lease liability payments	$m	0.0	(0.3)	(0.2)	0.0	0.0
Other	$m	(0.2)	0.0	(1.2)	0.0	0.0
Financing cash flow	**$m**	**2.3**	**(0.0)**	**17.1**	**0.0**	**0.0**
Cash year end	**$m**	**7.3**	**5.0**	**13.7**	**4.1**	**(4.9)**
Free cash flow	**$m**	**(2.5)**	**(2.3)**	**(8.4)**	**(9.6)**	**(9.0)**

Source: MST Access.

Thesis: Next-Gen Liquid Biopsies for Early Cancer Detection

Company Profile: Broad Portfolio of Liquid Biopsy Detection Technologies

INOVIQ (IIQ) is a development-stage diagnostic company developing and commercialising a broad portfolio of diagnostics and exosome-based solutions to diagnose cancer and other diseases.

EXO-NET – collaboration developing a test for the early detection of ovarian cancer through liquid biopsy, with potential wider implications. IIQ's EXO-NET represents the next generation of exosome isolation technologies. As such, IIQ is well positioned to support current efforts to harness the enormous potential of exosomes (small structures secreted by cells that contain a variety of 'cargoes' and are found in all bodily fluids) for use in a variety of research, diagnostic and therapeutic applications.

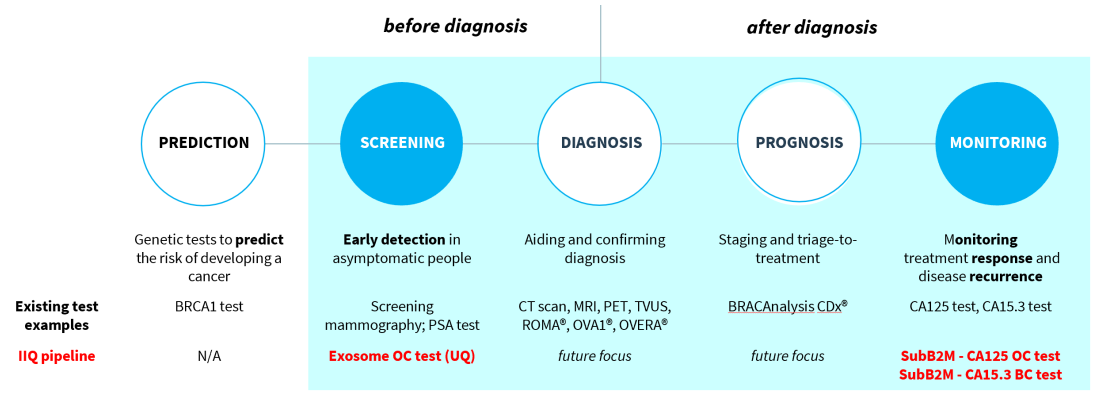
The technology is based on a proprietary solid-phase, 3-dimensional magnetic bead–based capture device that is rapid and scalable. Importantly, it can be customised to selectively capture a wide range of biological targets which provide information about the presence of a disease or condition.

IIQ has entered a research collaboration (including Licence Option) with the University of Queensland (UQ). The collaboration is working to develop a exosome-based liquid biopsy[1] test incorporating a clinical algorithm for early detection of ovarian cancer. The collaboration combines IIQ's EXO-NET capture technology and UQ's multiple biomarkers to develop a multivariate index assay (MIA) for early detection of ovarian cancer.

SubB2M – technology targets novel cancer biomarker found in ovarian and breast cancers at all stages – with potential for routine pan-cancer testing. This technology platform uses SubB2M, an engineered, highly selective ligand (recombinant protein), to bind to the biomarkers CA125 and CA15.3 decorated with Neu5Gc, a novel cancer biomarker that is elevated at all stages of ovarian and breast cancers and found at elevated levels in humans on tumour cells and tumour-associated molecules. IIQ recently engaged US-based CRO ResearchDx to advance IIQ's two lead products, the SubB2M-CA125 assay (for monitoring ovarian cancers) and SubB2M-CA15.3 assay (for monitoring breast cancers). IIQ is also evaluating a SubB2M-SPR test for detection of Neu5Gc as a potential pan-cancer biomarker for use in a general health panel. SubB2M-based tests have generated encouraging data; POC results vs healthy controls show SubB2M detects all cancer stages with >95%/100% sensitivity and 100%/100% specificity in breast/ovarian cancers, respectively.

hTERT and RUO EXO-NET: commercialised products. IIQ has commercialised two products to date: the hTERT test, an adjunct to urine cytology testing for bladder cancer, and RUO EXO-NET, a pan-exosome capture tool for use in research settings. The hTERT test was brought in through the merger with Sienna, whereas the EXO-NET research tool completed development and became available for sale in May 2021.

Exhibit 2: IIQ's pipeline of products is targeting multiple positions along the diagnostic continuum – from screening to monitoring



Source: INOVIQ.

[1] Liquid biopsy is a minimally invasive biopsy method that uses molecules in body fluids as biomarkers

Market Opportunity: Ovarian and Breast Cancers – High Unmet Need

The company's product development pipeline is well diversified across multiple cancers with high clinical unmet need providing multiple partnering opportunities. IIQ's most advanced programs aim to develop diagnostics for the early detection and monitoring of breast and ovarian cancers. The company expects monitoring tests to be available in 2HCY23. These two cancers represent huge opportunities. Five-year survival is drastically higher when ovarian and breast cancer is discovered in early stages, and both markets are enormous – projections are for the global breast cancer diagnostics market to reach $5.8 bn in 2025 (7% CAGR from current levels)[2] and the global ovarian cancer diagnostics market to reach US$2bn by 2026 (6.2% CAGR)[3].

Near-Term Catalysts (12 Months)

	EXO-NET	SubB2M
2HCY22	• New EXO-NET collaborations	
2023	• Secure partnering agreements • Progress results and development of exosome ovarian cancer test (UQ collaboration)	• Analytical validation (lab) • Clinical validation (lab) • Launch ovarian cancer test (LDT) • Launch breast cancer test (LDT)

Valuation

We value IIQ at A$195m or A$2.11 per share (undiluted), using a risk-adjusted net present value (rNPV) method to discount future cash flows through to 2043, consistent with the expiry life of current patent families. There are 9.3m options outstanding, exercisable at various prices. As such, our fair value of the shares on a fully diluted (101.4m shares) basis is A$1.92. This represents clear upside to IIQ's A$52m market capitalisation and A$0.57 share price. Our valuation uses a sum-of-the-parts approach, given the company's mix of assets, to arrive at a total rNPV of products (hTert and EXO-NET RUO) and development programs - SubB2M (Ovarian Cancer), SubB2M (Breast Cancer), and Exosome Ovarian Cancer screening test (collaboration with UQ) - of A$179m and net cash of A$15.3m as of 30 June 2022.

Risks – Typical Diagnostic R&D Hurdles

The company is currently advancing several technology platforms with a diversified portfolio of product candidates at different stages of development. As such, risks are less concentrated than many of its ASX peers. Nonetheless IIQ is subject to various sensitivities common to emerging innovative specialist healthcare companies engaged in diagnostic development. These include technology transfer risk, financing risk related to funding all programs, regulatory risk, competition, intellectual property, and commercialisation risk related to both reimbursement and adoption.

At a product level, major risks relate to the demonstration of efficacy, establishing clinical utility and meeting requirements of regulatory authorities across different jurisdictions. Given the current product pipeline, the main near-term risks relate to the commercialisation of the SubB2M tests in the LDT market.

Company History

INOVIQ, formerly BARD1 Life Sciences Limited, was founded in 2006 and listed on the ASX in 2016, raising $3m, to further develop and commercialise a blood test for the early detection of lung cancer based on autoantibodies to variant BARD1 proteins (isoforms) which are overexpressed in certain cancers. The test was the result of research conducted at the University Hospital of Geneva, Switzerland. The company's acquisition of Sienna Cancer Diagnostics in 2020 brought in two platform technologies (SubB2M and EXO-NET) and the commercialised product of hTERT. The company was rebranded INOVIQ, meaning 'intelligent innovation', in December 2021.

[2] Breast Cancer Diagnostics Market Size Reports, 2021-2028 (grandviewresearch.com) NB. includes imaging

[3] Ovarian Cancer Diagnostics Market Size Worth $2 Billion By 2026 (grandviewresearch.com)

Earlier, More Accurate Detection of Cancers with High Unmet Need

INOVIQ's (IIQ) investment case centres on the successful commercialisation of a broad portfolio of proprietary non-invasive diagnostic technologies that are being developed to address unmet needs for early detection of cancer when it can potentially be cured. These in the first instance include ovarian and breast cancers.

Aside from IIQ's two commercial products, the company's portfolio comprises three novel platforms which have the potential to address unmet needs and set new gold standards across multiple uses for cancer diagnosis. IIQ is using its EXO-NET platform technology to develop a portfolio of earlier and more accurate liquid biopsy tests, to be used for other conditions that leverage its ability for capturing exosomes and isolating biomarkers for use in diagnosis of metabolic, inflammatory, and neurodegenerative diseases.

Cancer Prevalence – Growing Given Ageing Population, Cancer Survivors

Cancer, defined broadly as the unchecked growth of cells, is the second-highest cause of death globally. In 2020, nearly 20m new cancer cases were diagnosed and about 10m deaths reported, worldwide[4]. According to estimates from the World Health Organization (WHO), cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries. This number is expected to grow given the number of new cancer diagnoses stemming from ageing of the population and greater number of cancer survivors overall.

Although both treatment of individual cancers and the understanding of their basic biology is improving, the mortality rate for many cancers remains high, highlighting the need to accurately detect the disease earlier when it has more treatment options and is potentially curable.

Importantly, the discovery of more specific cancer biomarkers and their combination in multivariate algorithmic approaches coupled with innovative laboratory methodologies are raising hopes of earlier cancer detection through non-invasive approaches using body biofluids (blood, urine and saliva) such as those being pursued by IIQ. Exhibit 3 summarises the cancers targeted by IIQ's product and development pipeline.

Exhibit 3: INOVIQ's portfolio is addressing cancers with high global incidence and mortality

Disease Type	Description	2020 New cases (est.)	2020 Deaths (est)
Ovarian Cancer	Ovarian cancer, in its most common form, develops in the cells that surround one or two of the ovaries. These cancers are difficult to detect in early stages, and often diagnosed when advanced and after it has spread to other parts of the body. Ovarian cancer is the leading cause of death from cancer of the female reproductive system.	313,959	207,252
Breast Cancer	Breast cancer is the second most common cancer in women after skin cancer. However, the incidence varies depending on ethnic background and age. In rare cases, it also occurs in men (< 1% of all cases). Mammograms can detect breast cancer early, possibly before it has spread.	2,261,419	684,996
Prostate Cancer	Prostate cancer is the most common cancer and the second leading cause of cancer death among men in the United States. Prostate cancer is often slow-growing and asymptomatic in early stages.	1,414,259	375,304
Pancreatic Cancer	Pancreatic cancer is often difficult to diagnose given a lack of validated, specific and reliable screening tests for early-stage pancreatic cancer in people who do not show clearly identified symptoms. As such, it is not typically found until later stages when the cancer can no longer be removed with surgery and/or has spread from the pancreas to other parts of the body.	495,773	466,003
Lung Cancer	Lung cancer includes two main types: non-small cell lung cancer and small cell lung cancer. Smoking causes most lung cancers, but nonsmokers can also develop lung cancer.	2,206,771	1,796,144
Bladder Cancer	The most common type of bladder cancer is transitional cell carcinoma, also called urothelial carcinoma. Smoking is a major risk factor for bladder cancer. Bladder cancer is often diagnosed at an early stage.	573,278	212,536

Source: GLOBOCAN, www.cancer.org.,www.cancer.net.

[4] https://pubmed.ncbi.nlm.nih.gov/33538338/: Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries

Cancer Staging – Early Diagnosis Improves Survival Rates, Health Economics

Measuring the extent or severity of a cancer begins with assessing its stage. The stage of a cancer describes how far cancer has spread in the body from its point of origin at the time of diagnosis and is used to determine treatment options. There are two major staging systems, although some cancers (e.g., lymphoma) have alternative staging. Typically, cancer is characterised according to the size of the tumour, the involvement of nearby areas and lymph nodes, and the absence or presence of distant metastasis and then assigned a stage expressed on a scale of 0 through 4 (see Exhibit 4). Stage 0 describes a non-invasive cancer that remains within its original location (in situ), while Stage 4 describes invasive cancers that have spread to other parts of the body.

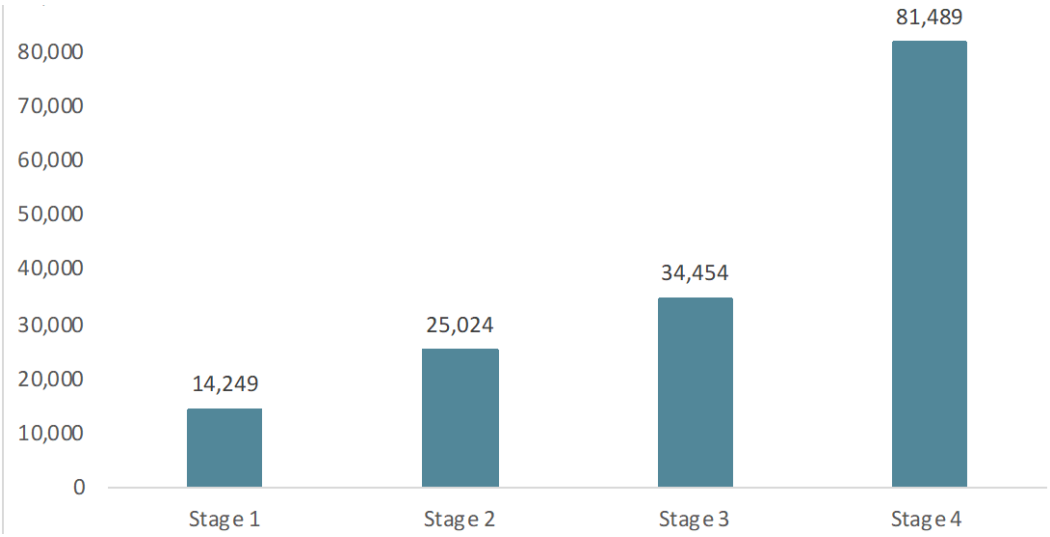
Exhibit 4: Key characteristics of each stage of cancer (most cancers have four stages[5])

Stage	Characteristics
1	Cancer is localised to a small area and has not spread to lymph nodes or other tissues.
2	Cancer has grown, but it has not spread.
3	Cancer has grown larger and has possibly spread to lymph nodes or other tissues.
4	Cancer has spread to other organs or areas of the body. This stage is also referred to as metastatic or advanced cancer.

Source: https://my.clevelandclinic.org/health/diseases/12194-cancer.

Early detection of cancer improves patient outcomes and significantly impacts the cost of treatment. Simply stated, the earlier the stage of diagnosis, the more treatment options are available, the less expensive cancer is to treat, and the better the patient's chances are for survival. Metastatic spread of cancer to distant sites remains the main cause of death for cancer patients in ~90% of cases[6]. Further, conventional cancer therapies are generally more effective with fewer side effects and better patient outcomes when introduced at earlier stages of the disease.

Exhibit 5: Estimated annual cost of breast cancer management (in USD), per disease stage



Source: The Economic Burden Associated with the Management of Different Stages of Breast Cancer – Alghamdi (2021).

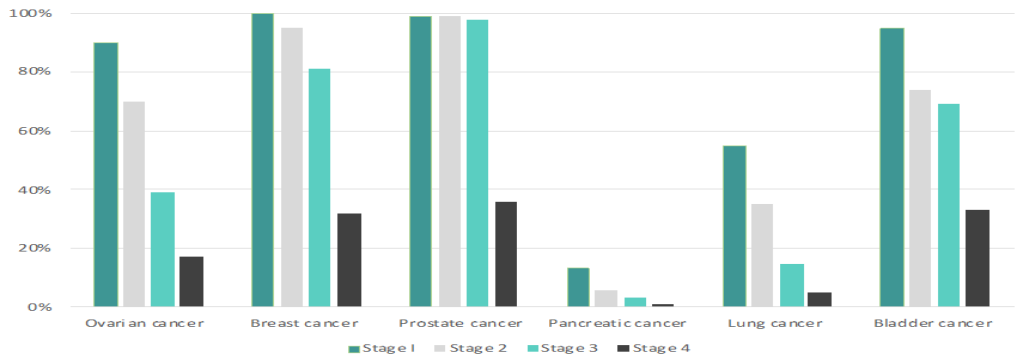
[5] https://www.cancer.net/navigating-cancer-care/diagnosing-cancer/stages-cancer
[6] A perspective on cancer cell metastasis. Science. – Weinberg (2011)

INOVIQ Targets Earlier Detection of Cancers with High Unmet Needs (<35% 5-Year Survival)

Blood-based tests using approved cancer biomarkers (see Appendix 2), such as proteins CA125 and PSA, have typically been used in the monitoring of patients undergoing treatment (during and after). However, the clinical utility of these tests is limited given insufficient sensitivity for early-stage cancer and the risk of false positives.

IIQ's product development pipeline is focused on developing in-vitro diagnostics (IVD) for early detection and improved monitoring of a range of cancers with high unmet needs, listed in Exhibit 6. These cancers are characterised as often asymptomatic in the early stages (Stages 1–2), with a rapid decline in survival rates when diagnosed at more advanced stages of the disease, of less than 30% at five years.

Exhibit 6: Cancer types and five-year relative survival rates (%) at stage of diagnosis



Source: www.cancerresearchuk.org.

Opportunity: Non-Invasive Precision Diagnostics in Early Cancer Detection

Cancer detection has many uses and areas of unmet need. The potential to identify asymptomatic cancer patients, improve health outcomes and lower the economic burden creates multiple opportunities for improving earlier cancer detection with new non-invasive tests and/or enhanced current standards. These can be viewed in terms of both (1) the indication for use along the diagnostic continuum and (2) the specific type of cancer. As such, IIQ is currently building on promising data rendered to date (sensitivity and specificity) and focusing its efforts on several key areas:

- improving existing single biomarker cancer monitoring tests using SPR immunoassays (CA125 in ovarian cancer, CA15.3 in breast cancer)
- developing novel exosome-based liquid biopsies for cancer screening in asymptomatic people (e.g., exosome-based test for ovarian cancer) and for early detection of other diseases (such as neurodegenerative diseases)
- developing a multi-cancer surveillance test for routine health check-up (SubB2M).

Exhibit 7: INOVIQ's collaboration and partnership agreements

Indication	Technology	Collaborator/Partner	Status	Notes
Ovarian Cancer	SubB2M - CA125	ResearchDx	Assay development	SubB2M/CA125 – transferred to ResearchDx for optimisation and validation
	EXO-NET	University of Queensland	Biomarker validation, early development	EXO-NET OC – collaboration with UQ to develop exosome-based test for early detection of ovarian cancer
	Bard1		Under review	
Breast Cancer	SubB2M	ResearchDx	Assay development	SubB2M/CA15.3 – transferred to REsearchDx for optimisation and validation
	Bard1		Under review	
Pan-Cancer	SubB2M		in-house research	
Prostate	SubB2M		in-house research	
Lung	Bard1		Under review	

Source: INOVIQ.

Product Portfolio:
Multiple Early Cancer Detection with Novel Blood-Based Tests

Clinical Strategy:
Setting New Standards in Diagnostics, Addressing Unmet Needs in Cancer

Performance characteristics of in-vitro diagnostics – sensitivity, specificity, and area under the curve

As diagnostic tools for detection of low concentrations of analytes (targets of interest), the clinical utility of any diagnostic is determined by several fundamental characteristics (Exhibit 8).

Exhibit 8: Measures of diagnostic performance

Parameters	Definition
Sensitivity	The ability of a test to correctly identify those patients with a disease
Specificity	The ability of a test to correctly identify those patients without a disease
Positive predictive value (PPV)	Out of all of the positive test results, indicates how many are true positives
Negative predictive value (NPV)	Out of all of the negative test results, indicates how many are true negatives
Area under the ROC curve (AUC)	Summary measure of accuracy, with closer to one result reflecting higher accuracy of the test.

Source: The Immunoassay Handbook 4th Edition – Wild.

The three interrelated components of INOVIQ's clinical strategy

(1) Improving specificity, sensitivity, and accuracy of existing single cancer biomarker tests across all stages. Data rendered to date for lead asset, the SubB2M ligand, shows 100% specificity and 100% sensitivity in detecting ovarian cancer and breast cancer using a highly sensitive SubB2M-based SPR test across all stages, boding well for IIQ's ability to transfer to routine assay platforms to improve on the specificity and potentially sensitivity of existing single cancer biomarker tests such as CA125 for ovarian cancer and CA15.3 for breast cancer.

(2) Targeting unmet need in early detection of cancers. Notably, there are no effective screening strategies currently available for ovarian, pancreatic, and prostate cancers (NB. PSA test still used for screening but no longer recommended for routine population screening by some). Further, many cancers, such as ovarian cancer, are characterised by minimal, general or entirely absent symptoms in earlier stages of the disease. Developing novel in-vitro diagnostics (IVDs) with higher specificity and good sensitivity for earlier detection of cancer addresses major unmet needs for many cancers that are typically asymptomatic and do not have existing approved screening tests.

(3) Developing earlier and more accurate blood tests with multi-cancer potential. Increasing clinical utility of liquid biopsies is raising hopes of a non-invasive and accurate alternative to tissue biopsies, as diagnostic for screening, diagnosis, treatment selection and monitoring of cancer. The process of capturing components from a tumour found in biofluid samples (mainly blood), which can then be analysed to provide comprehensive diagnostic information about a patient's tumour, is contingent on multiple factors including novel and informative biomarkers, analytically validated test design and clinically validated tests. IIQ is well advanced on all three fronts.

Key Value Drivers – Diverse Portfolio of Novel Biomarkers, Exosome Capture, and Multi-omics Approach

Detecting cancer at early stages significantly increases patient survival rates. However, mortality rates remain high for multiple cancers given the lack of tests for early detection and the poor false positive rates of current cancer-specific markers compounded by the lack of symptoms in early stages of the disease. IIQ's

portfolio of diagnostic and exosome-based solutions is focused on earlier detection, diagnosis, treatment selection and monitoring of cancer and other diseases using non-invasive liquid biopsy approaches. IIQ's multi-omics approach combines information from different types of biomarkers (e.g., protein and RNA) to improve test performance to better inform clinical decision making – the goal of precision medicine (see Precision Medicine Initiative[7]).

As such, the key value drivers in the IIQ technology portfolio relate to the following proprietary components:

- novel biomarkers and probes (SubB2M as the capture probe for the pan-cancer biomarker Neu5Gc; BARD1; hTERT)
- exosome-based capture and isolation platform (EXO-NET)
- multivariate index assays (EXO-NET/OCRF-7 ovarian cancer test collaboration with UQ).

Exhibit 9: Key value drivers in the IIQ technology portfolio

Platform	Mechanism et al	Types of specimen	Point of differentiation	Assay format
SubB2M	Highly specific probe that detects the pan-cancer marker Neu5Gc found in a range of human cancers.	Blood	Data rendered in SubB2M-based SPR test detect cancer across all stages in breast and ovarian cancers with >95% sensitivity at 100% specificity.	Surface Plasmon Resonance & Immunoassay
NETs	Biomarker capture technology for specific capture of target analytes from any biofluid.	Biofluids (blood, serum, urine)	EXO-NET® products utilize this technology for fast and efficient isolation of enriched exosome preparations for use in liquid biopsy tests.	Immunoassay/ Mulit-omics
BARD1	Biomarker technology covering various BARD1 tumour markers and methods of use for diagnostic applications.	Blood	Initial feasibility data showing high accuracy of BARD1 autoantibody tests for detection of ovarian, breast and lung cancers.	Immunoassay/plasma/serum/urine/saliva/cell culture
HTERT	Detecting hTERT (a component of telomerase) that is upregulated in most human epithelial cancers.	Urine	hTERT ICC test available in-market as an adjunct to urine cytology to assist the diagnosis of bladder cancer	Immunocytochemistry

Source: INOVIQ, MST Access. (*hTert is a revenue generating asset but not core to the company's future strategy)

Broad and Diversified Clinical Pipeline Built on Multiple Technologies

Multiple catalysts across product timelines: technologies from research to in-market

IIQ has a pipeline of proprietary (EXO-NET and BARD 1 for OC, BC) and licensed[8] (SubB2M, BARD1 in lung cancer) platform technologies with diagnostic applications in various stages of development, and collaborative partnerships with several leading academic/research institutes. In addition to its two products in market – a product for bladder cancer and an exosome capture tool – the company's product pipeline is targeting high unmet medical need in oncology for early detection and monitoring of several cancers with the most advanced in ovarian and breast cancers. IIQ's pipeline also includes early-stage diagnostic research programs in the areas of pancreatic, lung and prostate cancers.

Recently announced contracts and collaborations with US-based ResearchDx[9] and the University of Queensland (UQ) should accelerate development of its SubB2M and EXO-NET platforms for diagnostic applications. Management targets registration of two immunoassay products for monitoring of ovarian and breast cancer in 2HCY23. INOVIQ's clinical development pipeline spans several platforms targeting both monitoring and detection of several cancers with high unmet need, namely breast, ovarian, prostate and pancreas (Exhibit 10).

Exhibit 10: INOVIQ's broad development pipeline provides clinical optionality and partnering opportunities

Product	Indication	Platform	Use	Research	Assay Development	Clinical Development	Registration	In Market
Exosome-OC (OCRF-7)	Ovarian Cancer	Mulitomic	Screening					
SubB2M-OCM	Ovarian Cancer	Immunoassay	Monitoring				2023	
SubB2M-BCM	Breast Cancer	Immunoassay	Monitoring				2023	
SubB2M-PCS	Prostate Cancer	Immunoassay	Detection					
SubB2M-PaC	Pancreatic Cancer	Immunoassay	Detection					
BARD1-Ovarian	Ovarian Cancer	Immunoassay	Detection					
BARD1-Breast	Prostate Cancer	Immunoassay	Detection					
BARD1-Lung	Lung Cancer	Immunoassay	Detection					
hTERT	Bladder Cancer	ICC	Adjuncty to cytology					
EXO-NET-RUO	Exosome Capture	Device	Research tool					

RUO= Research Use Only, ICC = immunocytochemistry

Source: INOVIQ

[7] https://obamawhitehouse.archives.gov/precision-medicine

[8] BARD1 lung cancer IP licensed from UNIGE, rest owned

[9] ResearchDx is a California-based Contract Diagnostics Organization (CDO) that offers a complete range of in vitro diagnostics services

EXO-NET® Technology: Harnessing Power of Extracellular Vesicles

The Potential of EVs: Carriers of Biological 'Messages in a Bottle'

Extracellular vesicles (EVs) are lipid-bound vesicles which are released by all cell types, carrying precious cell-derived biomolecules, including nucleic acids (RNA and DNA), lipid, proteins, and metabolites. EVs are found in all biofluids and are involved in cell-to-cell communication and cell maintenance between local and distant cells. The delivery and uptake of their 'cargo' by other recipient cells facilitates both normal physiological and pathological (disease) processes in these other cells. EVs and their cargo represent valuable sources of critical information, with potential uses in both diagnostics (transport carriers of biomarkers) and therapeutics (optimising active cargo for drug delivery, and/or intrinsic properties related to cell of origin).

Exosomes – tiny carriers of biomolecular material have great potential, given their many roles as messengers of health and disease

Exosomes are a type of small EVs which are found in various body fluids and secreted by all cells in the body. Exosomes communicate with other cells and regulate their function. A specific inward budding formation process (see 'The science of exosomes', next page) packages active cargo (proteins, nucleic acids, and lipids) from parent cells and delivers it to other neighbouring or distant cells and alters the function of recipient cells with cargo (e.g., healthy, or diseased) of instructions that are to be communicated to other cells. By capturing exosomes using EXO-NET, their molecular information can be used to identify changes in the cell's function and the early onset of diseases, including cancer.

The clinical utility of exosomes stems from their safety, biocompatibility, low immunogenicity, presence in most biofluids (plasma, serum, urine, saliva, semen, cerebral spinal fluid (CSF), breast milk, and amniotic fluid), ability to permeate tissue including the blood-brain barrier due to their small size, high biological stability, and different biological functions given different parent cells. Many varied biomolecules have been identified from exosomes (4,400 proteins, 194 lipids, 1,639 mRNAs, 764 miRNAs), highlighting the complexity of information carried and diversity of roles performed. These pathways can be used for therapeutic interventions, and the cargo carried by exosomes can be altered to deliver therapeutic agents.

Clinical applications of exosomes: research uses, disease identification (diagnostics) and treatment (therapeutics)

Diagnostics – Exosomes derived from different cell types have different functional characteristics given both their 'cargo' of specific proteins, lipids, and nucleic acids[10] and transmembrane proteins or nucleic acids of the exosome lipid membrane itself. As such, exosomes carry rich sources of information about their origin (parent) cell. This supports the use of exosome-based biomarker approaches to understand the underlying pathology of different types of parent cells (e.g., liver, ovaries, heart, blood, brain). Further, the composition of secreted exosomes can change as different pathologies progress, making the detection of variations valuable as diagnostic and prognostic biomarkers as well as potential therapeutic targets of disease. **Therapeutics –** Beyond diagnostics, exosomes have shown potential as drug delivery systems stemming from their capacity to deliver complex payloads. This, along with their ability to interact with and be taken up by target cells, has raised hopes of using exosomes as targeting carriers of therapeutic drugs.

The technical hurdles – why the potential of exosomes has not yet been fully realised

The two main hurdles to date for the clinical use of exosomes generally (and liquid biopsy techniques in particular) have been to efficiently: (1) **scale the extraction process** to ensure optimal and reproducible enrichment and yield for the reliable measurement of biomolecules of interest (e.g., tumour-derived exosomes); and (2) **separate exosomes of interest** from other EVs and biomolecules of similar size. This has led to a lack of standardisation, source heterogeneity and source matrix complexity and reproducibility. Various methods have been used over the past decade; however, no practical technology can currently isolate EVs completely from other non-EV components. Factors include the complexity of biological fluids; the considerable overlap of the physicochemical and biochemical properties among the exosomes, lipoproteins, virus, and other EVs; and the heterogeneity of exosomes themselves[11].

[10] Exosomes: biogenesis, biologic function, and clinical potential. Zhang et al (2019)

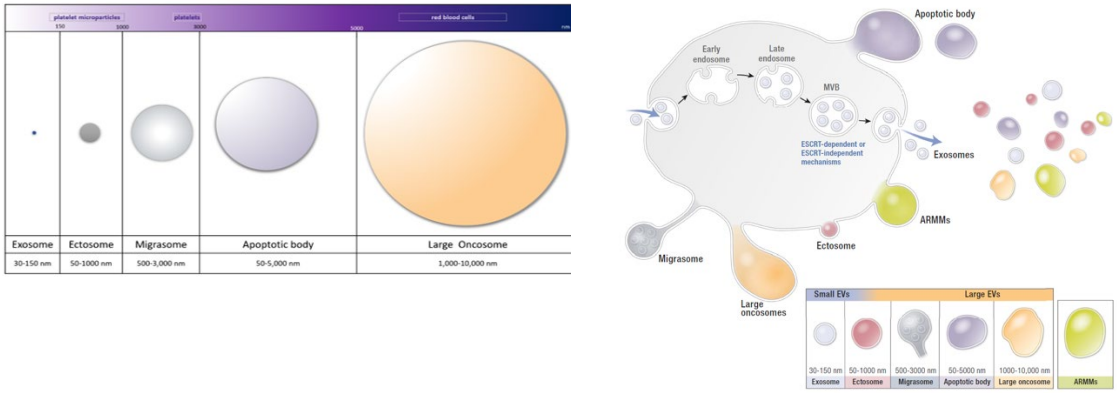
[11] Progress, opportunity, and perspective on exosome isolation - Efforts for efficient exosome-based theranostics: Yang et al (2020)

The science of exosomes

Extracellular vesicles and exosomes – what are they, and what do they do? The term 'extracellular vesicle' was first coined in the 1970s to describe non-replicating semi-spherical vesicle structures secreted by cells into the extracellular space. EVs play an important role in the communication between cells in both healthy and disease settings. They have been found in all bodily fluids, including plasma, urine, milk, tears, sweat and semen, as well as in the plant kingdom and in micro-organisms.

EVs comprise a core containing a variety of cargoes such as nucleic acids, lipids and proteins associated with the cell's plasma membrane, encapsulated by a lipid bilayer membrane. EVs can be categorised by size – small and large, with exosomes being the smallest.

Exhibit 11: Relative sizes of EVs – exosomes are tiny (left); The formation of exosomes (right)

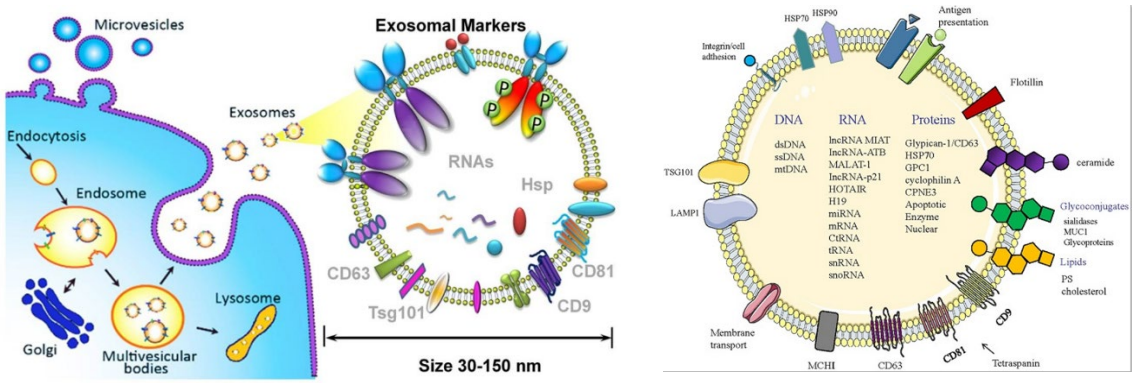


Source: Extracellular Vesicles and Their Emerging Roles as Cellular Messengers in Endocrinology: An Endocrine Society Scientific Statement, Salomon et al (2022).

How exosomes develop (biogenesis) and obtain their information-filled 'cargo'. Exosomes, a type of small EV, typically range from 30 to 150 nm in size. They are generated in several steps.

- The cell buds inward, creating a body called an 'endosome' inside the cell.
- Within the endosome, the internal budding process continues, filling it with tiny 'intraluminal vesicles'. As these vesicles are created, they are loaded with their 'cargo': nucleic acids (DNA, mRNA, miRNA), proteins and lipids.
- The loaded intraluminal vesicles are now called 'exosomes', and the endosome is now a 'multivesicular body' (MVB). The MVB, containing exosomes, is trafficked to the cell's plasma membrane. The MVB and plasma membrane fuse, releasing the exosomes with their cargo into the extracellular space (Exhibit 12).

Exhibit 12: Exosome biogenesis (formation), properties, and molecular composition



Source: Microfluidic Exosome Analysis toward Liquid Biopsy for Cancer; He et al (2016), https://www.jcancer.org/v12p5035.htm

EXO-NET® Technology: Design and Functionality – Overcoming Hurdles to Power Clinical Applications

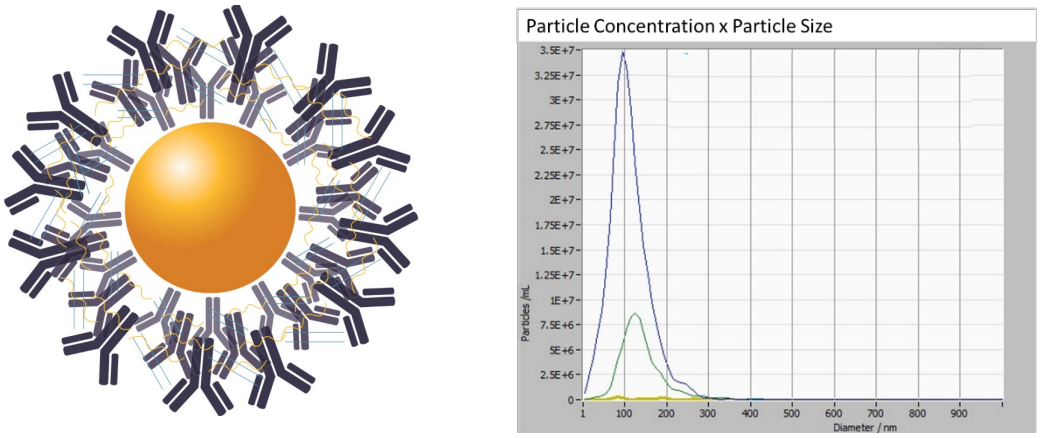
Innovative design – flexible, customisable, and compatible with other test formats

IIQ's EXO-NET® is a proprietary magnetic bead–based immunoaffinity capture technology for isolating EVs, including exosomes, from small clinical sample volumes of biofluids.

Magnetic bead–based capture of specific targets is a well-established and proven technology. However, IIQ has adapted this approach to build an exosome capture system, using a panel of monoclonal antibodies in a proprietary three-dimensional matrix (EXO-NET®) constructed on nanobeads (see Exhibit 13).

Unlike other magnetic bead constructs using single layers of antibody molecules, EXO-NET® is composed of a collection of exosome-specific antibodies covalently linked to form a 3D multilayered antibody matrix. This matrix construct has been shown to increase binding avidity and analyte capture and outperform the more time-intensive ultra-centrifugation methods, which to date have been considered the gold standard. EXO-NET captures 75% of small EVs (exosomes) from samples (e.g., cell-condition medium - see Exhibit 13).

Exhibit 13: EXO-NET® technology: (conceptual schematic– left); EXO-NET captures 75% of small EVs (right)

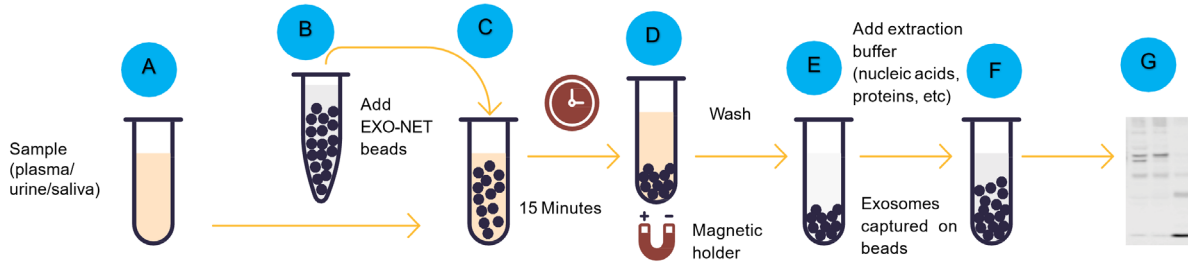


Source: INOVIQ. NB. Difference between blue (original) and green peak represents exosomes captured by EXO-NET®

How it works: EXO-NET® captures EV targets in 4 simple steps

The technology comprises a proprietary molecular matrix, made of antibodies, designed to capture targets of interest (wide range of EVs from different cell types), which is applied to magnetic beads (nanobeads). The use of the three-dimensional matrix increases the density and surface area occupied by the antibodies, thereby increasing the accessibility of ligand binding sites and extraction efficiency. The antibody matrix attached to these beads has been designed to capture a wide range of EVs from different cell types. IIQ can customise the mix of antibodies in the matrix to capture different types of exosomes.

Exhibit 14: EXO-NET® – workflow for exosome capture within 15 minutes



Source: INOVIQ.

The Competitive Advantages of EXO-NET®: Rapid, Efficient, Pure, Scalable

Immunomagnetic bead capture scores highly vs commonly used EV isolation techniques

The recent Endocrine Society Scientific Statement reported that immunomagnetic bead capture approaches were found to outperform commonly used EV enrichment (isolation) techniques when assessed using the key features of:

- time: length of operation time
- cost: cost of the equipment and consumables
- scalability: the ease of scaling the technique to process large volumes of fluids
- recovery (yield): the percentage of EVs in fluids that could be extracted (yield)
- specificity: ratio of EVs extracted relative to total protein.

Exhibit 15: Comparison of the key features in commonly used extracellular vesicle enrichment techniques

EV enrichment techniques	Time	Cost	Scalability	Recovery	Specificity
PEG precipitation	+++	++++	++++	++++	+
Size exclusion chromatography	+	+	+	+	+++
High MW centrifugal filters	++++	+++	++++	+++	++
Differential ultracentrifugation	+	++	+	+	++
Tangential flow filtration	+++	++	++++	+++	+++
Affinity chromatography	++	+	++	++	++++
Immunomagnetic bead capture	++++	+++	++++	+++	++++

Source: Endocrine Reviews: Salomon et al (2022). (+ denotes the desirability of the feature, from +: least to ++++: most desirable).

EXO-NET® technology advantages suggest it's a 'best-in-class' EV isolation system

Major technological advantages of EXO-NET® include:

- rapid isolation of an enriched population of EVs from any biofluid (within 15–20 minutes)
- cost effective to use (avoiding time-consuming workflows of the current gold standard methods)
- scalable for high-throughput sample processing and can be fully automated
- flexible enough to be deployed on most lab test modalities (well plates, polymer beads, magnetic beads, and lateral flow devices)
- higher yield: recovery by isolating intact EVs results in higher yield of useful targets
- highest purification of exosomes eliminating contaminants and reducing background noise
- simple (4 steps) and compatible with downstream testing formats (fluorescence-activated cell sorting [FACS], solution array and ELISA)
- customisable: EXO-NET is designed to capture a wide range of biological targets subject to proteins that are present on their surface being recognised by the capture ligands incorporated in the matrix (or NET) which can be adjusted.

Good Manufacturing Practice (GMP) compliance also underpins competitive advantage

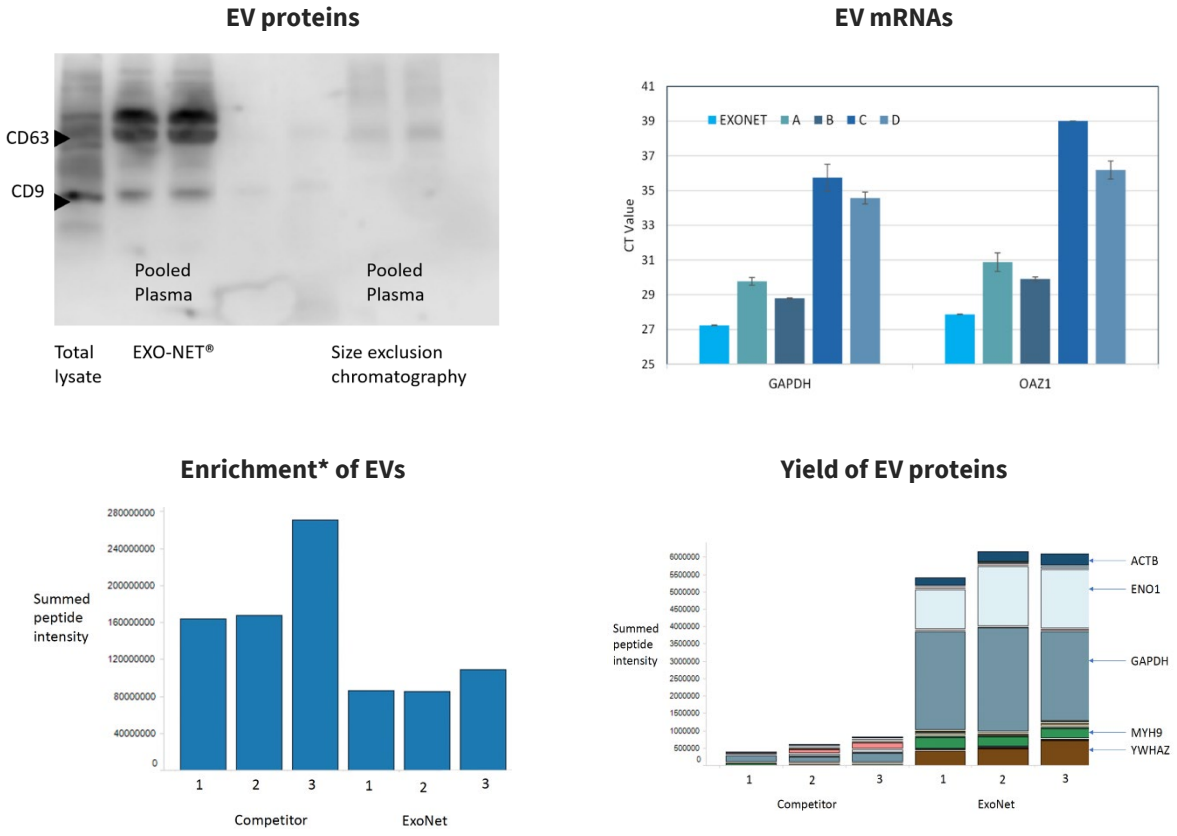
The ability to scale the process for large volumes of fluids, combined with the time saved compared to other methods, should support high throughput requirements of most commercial laboratories. The company is in the process of converting its main lab in Australia to GMP[12] standards. As such, clinical and large-scale production of EXO-NET® under GMP-compliant standards would differentiate EXO-NET® and provide a clear competitive advantage for all future applications of the technology.

[12] Good Manufacturing Practice (GMP) is a system for ensuring that products are consistently produced and controlled according to a set of prescribed quality standards.

EXO-NET® Outperforms Competitors in Benchmark Studies of Yield & Purity

EXO-NET® has been found to be equivalent to or outperform all major competitor products tested to date (see Exhibit 16).

Exhibit 16: EXO-NET vs. competitors in purity studies



Source: INOVIQ. *Higher summed peptide intensity of Albumin in competitor beads (~double), therefore less pure.

Current Commercial Strategy: Leverage EXO-NET® Advantage in Exosome Isolation and Purification

EXO-NET® (RUO) launched for research use – building a commercial position

The EXO-NET® (RUO) pan-exosome capture tool was designed to isolate a broad range of exosomes from multiple tissues, cells (cell culture), and body fluids (plasma, sera, urine, and saliva). IIQ's May 2021 launch of EXO-NET® (RUO) for use in research settings introduced the product to the market, established a brand position and raised awareness of EXO-NET® among key opinion leaders in the exosome space. Further, IIQ recently engaged a US sales team.

Early detection of ovarian cancer: first diagnostic application of EXO-NET®

The first move into diagnostics is now underway with the University of Queensland (UQ) collaboration to develop an exosome-based screening test for early detection of OC. IIQ plans to build alliances that validate the use of EXO-NET® in exosome-based applications across multiple indications, commencing with cancer.

In April 2022, IIQ entered an expanded collaboration with UQ to develop a exosome-based ovarian cancer screening test, a potential world first. This is IIQ's first foray into diagnostic applications using EXO-NET®.

Exhibit 17: UQ collaboration: EXO-NET technology in ovarian cancer (diagnostic application): at a glance

Mechanism	Uses exosome-specific antibodies to capture specific cancer-derived exosomes
Development status	Collaboration with University of Queensland for development of multivariate index assay for the early detection of ovarian cancer
Clinical area of focus	Ovarian cancer - early detection
Milestones and next steps	(1) Confirmation that the biomarkers currently included in the OCRF7 algorithm are captured by EXO-NET and are informative of disease status. (2) Identify any additional informative biomarkers that are captured by EXO-NET. (3) Finalise the composition of the test algorithm. Lock algorithm and SOP (4) Establish test performance in an independent retrospective case:control study (5) Establish test performance in a large cohort trial (6) Establish test performance in longitudinal cohort

Source: INOVIQ.

Contribution from each party in the collaboration: IIQ's collaboration with UQ effectively combines:

- EXO-NET® technology to isolate specific exosomes from biofluids (plasma in this case)
- UQ's intellectual property:
    - a set of validated exosomal protein and micro-RNA (miRNA) biomarkers
    - a proprietary algorithm which had previously shown over 90% accuracy in detecting Stage 1 and 2 ovarian cancers in an independent retrospective study.

UQ selects EXO-NET® technology based on performance and commercial attributes: Previously, researchers at UQ identified and validated exosomal protein and micro-RNA (miRNA) biomarkers (identified using a different exosome isolation method) that, combined in the OCRF-7 algorithm, showed over 90% accuracy in detecting Stage 1 and 2 ovarian cancers in an independent 500-sample retrospective case-control study. An initial evaluation by UQ of the EXO-NET® pan-exosome product, benchmarked to in-house chromatography method, based on size, for isolation of the relevant exosomal biomarkers, found EXO-NET® equivalent or better than its in-house isolation method in terms of simplicity and speed.

Further, EXO-NET brings two additional elements to the project:

- a feasible pathway to commercialisation, as EXO-NET® is compatible with routine path lab workflows
- the capture of a more enriched and defined sub population of exosomes, providing the opportunity to identify additional informative biomarkers to include in the OCRF7 algorithm to detect ovarian cancer earlier.

Timeframe, financing and milestones: The project has a duration of four years, with multiple readouts expected over that period, and is supported by a $2.7m grant awarded by the Australian government's Medical Research Future Fund. The clinical validation component of the study will be performed at UQ using EXO-NET® to isolate exosomes from blood samples collected from the UK Collaborative Trial of Ovarian Cancer Screening (a major bioresource resulting from one of the world's largest randomised controlled trials in ovarian cancer screening).

IIQ has an exclusive option to license UQ's intellectual property to develop and commercialise the exosome-based ovarian cancer screening test. The Umbrella Research Agreement also allows the parties to collaborate on other exosome-based research projects.

Longer-Term Commercial Applications: Research, Diagnostics, Therapeutics

The company's longer-term strategy, underscored by current efforts to meet GMP compliance standards in the Australian lab facility, seeks to leverage EXO-NET®'s competitive advantage in exosome isolation and capitalise on emerging opportunities for exosome-based products in diagnostic and therapeutic applications.

Research applications: EXO-NET® (Research Use Only)

The ability to customise EXO-NET® research tools to isolate tissue- and cell-specific exosomes and biofluids for use in targeted applications supports further commercial opportunities in research.

Diagnostic applications: EXO-NET® redefines liquid biopsy clinical utility

Exosomes and their cargo are rich sources of clinically relevant diagnostic information (given they contain DNA, RNA, protein, lipid, sugar structures and metabolites) and are ideally suited for use with the emerging field of molecular profiling of biofluids, knows as liquid biopsy.

Although several liquid biopsies have been developed and commercialised, tissue biopsies are still considered the gold standard for comprehensively diagnosing a patient's disease type and stage. Nonetheless, liquid biopsy approaches are gaining ground with applications in reproductive health, cancer, and transplant medicine. In cancer, they offer a simple and non-invasive alternative to tissue biopsy–based diagnostic methods and are potentially better suited to early detection and therapeutic selection strategies.

Liquid biopsy has several unique advantages in cancer care when compared with tissue biopsy:

- it is non-invasive and safe, avoiding the complications of tissue biopsy, which in cases such as brain and late-stage lung cancer can be challenging, and avoids infection and other issues associated with healing
- it provides an opportunity to dynamically monitor tumour-specific alterations that may be missed in other assessments. These include heterogenous tumour cells that appear in regional parts of the body
- it enables repeated sampling and therefore real-time information for clinical decisions
- it allows long-term monitoring of minimal residual disease or remaining disease after treatment
- it provides opportunities to discover new biomarkers and hallmarks of disease.

Advantages of exosomes as high-grade and enriched sources of data to supercharge liquid biopsy. The three main sources of information currently used in liquid biopsy techniques are:

- cell-free DNA (cfDNA): cfDNA are nucleic acid fragments released into bloodstream during apoptosis, or necrosis, of cells. DNA is a very stable molecule, and cancer-derived cfDNA can be highly enriched in plasma. As such, cfDNA has proven a popular metric for blood-based liquid biopsies in cancer.
- circulating tumour cells (CTC) which are shed from both primary and metastatic tumours are another source of data but are extremely rare compared with other cells in the blood of patients with cancer[13].
- exosomes and other extracellular vesicles: Exosome formation enables the capture of complex intracellular molecular cargo, including cfDNA (in plasma exosomes). As such, exosomes and their cargoes provide rich sources of more comprehensive data that could be used to improve detection and power of liquid biopsies. Exosomes offer three key advantages over other sources of liquid biopsy:
    - high biological stability
    - presence in high concentrations in various body fluids
    - secreted by living cells and contain biological information from the parental cells versus cfDNA, which is secreted during necrosis or apoptosis.

Despite the advantages and commercialisation of exosome-based liquid biopsies, issues of exosome isolation, with high efficiency and at scale, has hampered progress. IIQ addresses these technical hurdles with EXO-NET®.

We think more convenient methods of exosome isolation that don't compromise purity and integrity of isolate, such as EXO-NET, will drive discovery of biomarkers, clinical utility and adoption of liquid biopsies.

Exosomes as biomarkers – multiple applications stemming from enabling of liquid biopsy. Studies have shown that exosome secretion is increased under pathological conditions such as inflammation, immune response, neurodegeneration, cancer, cell death and angiogenesis. Further, proteomic analysis of exosomes secreted under these conditions has shown significant changes in protein expression. This has generated tremendous interest and research into the use of exosomes as diagnostic biomarkers across a broad range of diseases, including:

- cancer
- neurodegenerative disorders
- cardiovascular disease
- metabolic disorders (such as diabetes)
- inflammatory conditions.

[13] Circulating tumour cells and DNA as liquid biopsies in gastrointestinal cancer, Nordgard et al (2017)

Cancer diagnostics – multiple indications. The pairing of exosomes and liquid biopsies has been popular in cancer diagnosis and treatment. The continuous secretion of exosomes by tumour cells makes them ideal for liquid biopsy applications requiring frequent sampling compared with more invasive and dangerous surgical tissue biopsies. Notably, metastasis formation is the leading cause of death in cancer patients. Evidence suggests, tumour-derived exosomes play an important role in preparing distant microenvironments (premetastatic niche) in the metastatic process, making them particularly valuable as potential cancer biomarkers (see Exhibit 18).

EXO-NET®'s ability to capture more enriched and defined subpopulations of exosomes provides the opportunity to identify additional and more informative biomarkers vs other exosome isolation methods. This ability is especially relevant given the heterogeneity of cancer cells and the diversity of exosomes.

Exhibit 18: Examples of EV proteins that have been identified as potential biomarkers for cancer

Biofluid	Exo-protein/tumor biomarker	Tumor type
Plasma	PSA	Prostate Cancer
	TRPC5, TGFβ1	Breast Cancer
	CD24, EpCAM, CA-125, TGFβ1, MAGE3/6, Claudin-4	Ovarian Cancer
	EpCAM	Pancreatic Cancer
	CD171, NY-ESO-1, PLAP, Flotilin1	Lung Cancer (NSCLC)
	Caveolin-1, CD63, TYRP2, VLA-4, HSP70, HSP90, PDL-1	Melanoma
Urine	PSA, PSMA, δ-catenin	Prostate Cancer
	EH-domain-containing protein 4, EPS8L1, EPS8L2, GTPase NRas	Bladder Cancer
	MMP9, DKK4, EMMPRIN, CP, PODXL, CAIX, CD10, AQP1, dipeptidase 1, syntenin 1	Renal Cancer
	LRG1	Lung Cancer (NSCLC)
Serum	MDR-1/P-gp, MDR-3, PABP4	Prostate Cancer
	Survivin, Survivin2B, UCH-L1, HER2	Breast Cancer
	GPC1, CKAP4, MIF	Pancreatic Cancer
	EGFR, EGFRv, CD63	Glioblastoma
Ascites	CD24, EpCAM	Breast Cancer
	E-cadherin, MMP2, MMP9, uPA, CD24, L1CAM, ADAM10, EMMPRIN	Ovarian Cancer
	Claudin-3	Colorectal Cancer
Plasma/Serum	Survivin	Prostate Cancer
	CD82	Breast Cancer

Source: Liquid Biopsy in Cancer Patients Giordano et al (2017).

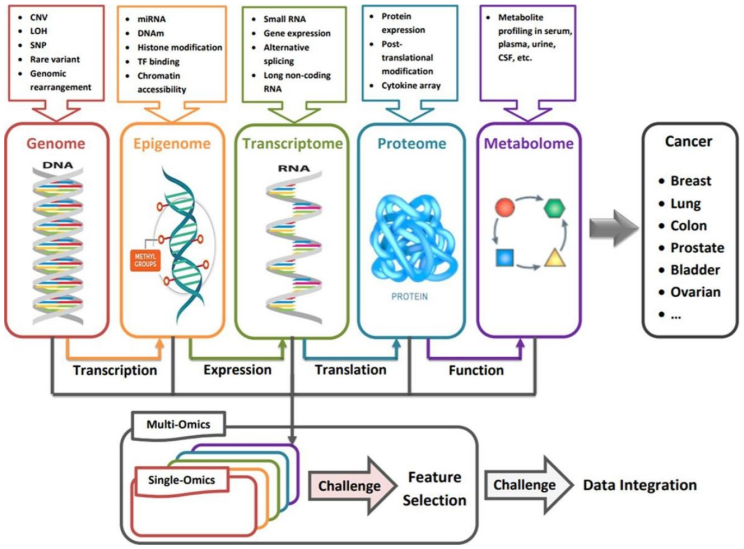
Multi-omics adds precision to cancer diagnostics and focus on exosome sample quality. Multi-omics in cancer diagnostics involves the use of multiple biological analytical techniques combined with multivariate statistical methods of data analysis.

This means that one sample can be analysed for multiple biomarkers and across a range of data sets (comprehensively). It can also interpret large volumes of data (at scale) to uncover new pathways, biomarkers, and drug targets.

Data mining the sample. Application of multi-omics approaches is improving the understanding of the cellular-level biology of human disease, as well as the precision of clinical diagnosis, prognosis, and treatment. In cancer, integrating multiple technologies is improving cancer sub-type profiling, identifying biomarkers associated with biological processes to support identification of actionable therapeutic targets, tracking progression of disease and treatment (treatment selection, treatment monitoring and recurrence monitoring) and increasing the utility of liquid biopsy.

EXO-NET®, given its advantages and the growing demand for high-quality exosome samples, in combination with liquid biopsy testing, should benefit from this more targeted approach. Notably, IIQ is using this approach for screening and diagnostic of ovarian cancer in its collaboration with UQ.

Exhibit 19: Multi-omics: integration of multiple analytical techniques for a more comprehensive view



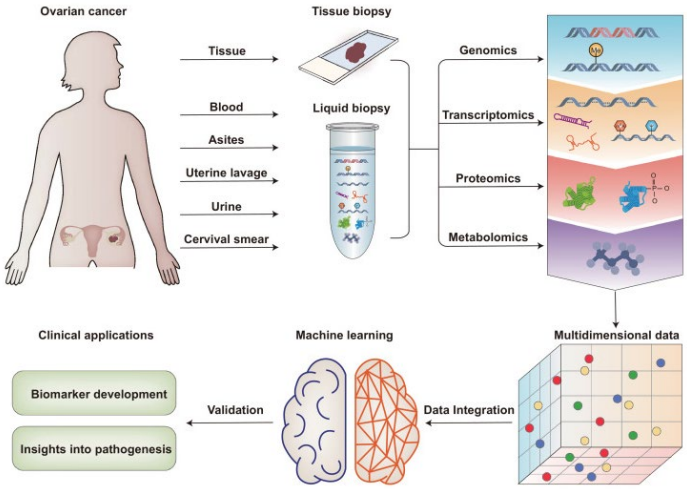
Source: A survey on single and multi-omics data mining methods in cancer data classification: Momeni et al (2020).

The 'omics' in multi-omics

Genomics (complete set of genetic information). Genomic sequences were the first widespread omics data available for understanding human cancer biology and pathogenesis. Genomics is typically the starting point in establishing a relationship with specific genetic variants. Over the top of this is:
Epigenomics (processes that regulate expression of genes). Changes include chemical modifications such as methylation and acetylation of DNA and/or DNA-binding histone proteins that affect expression.
Transcriptomics (messenger RNA) techniques are engaged in the detection of the presence and quantification of RNA transcripts, especially mRNAs, but can also be extended to other types of noncoding RNA transcripts such as long noncoding transcripts (LncRNAs) and microRNAs.
Proteomics (proteomes) focuses on an individual's full set of proteins and their post-translational modifications such as glycosylation.
Metabolomics (chemical processes involving metabolites) focuses on changes to metabolite levels caused by the growth of the cancer.

Source: Onco-Multi-OMICS Approach: A New Frontier in Cancer Research: Chakraborty et al (2018).

Exhibit 20: Schematic representation of multi-omics approaches towards biomarker discovery for early diagnosis in ovarian cancer (this approach applies to multiple cancers)



Source: Multi-omics approaches for biomarker discovery in early ovarian cancer diagnosis: Xiao et al (2022). NB: ascites (sic)

Companion assays and companion diagnostics – adding precision to precision medicine. We see IIQ as well placed to become an industry leader and to advance the development of exosome-based liquid biopsies through the out-licencing of EXO-NET®, as well as the development of its own diagnostic products.

Harnessing biological information from exosomes more efficiently and at scale, using EXO-NET®, should drive discovery of new diagnostic exosome biomarkers and allow for more efficient harvesting of known biomarkers for use in liquid biopsies. We expect this to expand commercial opportunities across multiple indications. These include the identification, and stratification, of suitable patients and/or the development of assays to support clinical trials of targeted therapies.

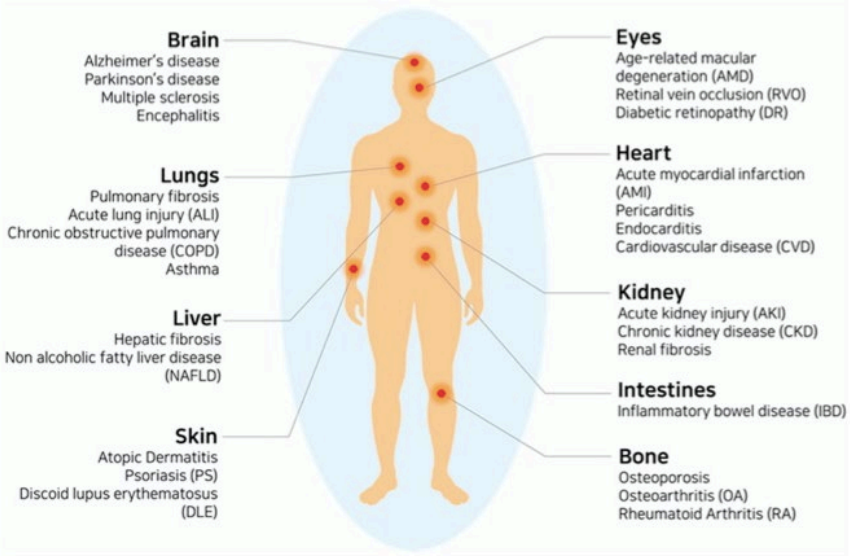
This also opens the door to opportunities for partnering as a companion diagnostic manufacturer and lays the foundation for a move into therapeutics on a standalone basis.

Exosomes as novel biomarkers of multiple diseases. The enormous potential of exosomes for use in both diagnostic and therapeutic applications stems from the fact that they are secreted by all living cells (healthy and diseased) and can transport complex payloads, reflecting the cell of origin, containing nucleic acids (such as mRNA and miRNA), functional proteins, lipids, and other metabolites to act specifically through membrane fusion on close as well as distant recipient cells to mediate biological pathways. Increasing understanding of this targeted messenger function in the regulation of fundamental pathophysiological processes is fuelling interest and research into exosomes as potential biomarkers for a multitude of associated diseases.

Inflammation – underpins multiple diseases and is mediated by exosomes. The most important of these, given its link to cancer is inflammation. The role of exosomes in mediating inflammation is linked to their ability to carry modulators that promote inflammation and change the microenvironment in distant target tissues. In cancer, exosomes derived from tumour cells promote metastatic development through inflammation and pre-emptively prepare distant micro-environments in the body for growth of metastasis. There is also evidence that inflammation can interfere with the body's immune system and hamper immune surveillance and lead to resistance to therapy.

Inflammatory processes mediated by exosomes also play a pivotal role in many other pathologic states including inflammatory bowel disease, type 2 diabetes, arthritis, obesity, kidney disease, rheumatoid arthritis, and neurodegenerative diseases (see Exhibit 21).

Exhibit 21: A schematic of the human body with inflammatory diseases



Source: Suh, J.H.; Joo,H.S.; Hong, E.B.; Lee, H.J.; Lee, J.M. Therapeutic Application of Exosomes in Inflammatory Diseases. *Int. J. Mol. Sci.* 2021, 22, 1144. https://doi.org/ 10.3390/ijms22031144.

Cardiovascular and related risk indications. The role of exosomes in cardiovascular and metabolic diseases shares characteristics with their role in cancer. Exosomes derived from cardiac, endothelial, and vascular smooth muscle cells hold a range of miRNAs, which may be transferred to recipient cells, leading to changes in their function. Exosomal miRNAs have been shown to play a damaging role in CVD, including atherosclerosis, preeclampsia, hypertension, heart failure and ischaemic heart disease.

Exhibit 22: Exosome biomarkers for both cardiovascular disease and related risk factors

Biofluid	Exosome Molecules	Disease indication
Plasma	miR-1, miR-208a, miR-133a, miR-499-5p, miR-223, miR-339, miR-21	Coronary Artery Disease
	miR-326, miR-532-5p, miR-186, miR-127-3p, let-7g, let-7d, miR-126	Type 2 Diabetes
	hsa-miR-16-5p, hsa-miR-4459, hsa-miR-451a, hsa-miR-6510-5p	Obstructive sleep apnea
	miR-1, miR-23a, miR-24, miR-92a, miR-126, miR-133a	Coronary artery bypass graft
Serum	MYBPC3, VIM	Coronary Artery Disease
	miR-122-5p, let-7a-3p, miR-26b-3p, miR-193b-5p, miR-4532, miR-432-5p	Type 2 Diabetes
Urine	NCC, AIG-2, SDCBP, NKCC2, TSC, ACTB, RAIG-3	Hypertension

Source: Exosome-Derived Mediators as Potential Biomarkers for CV Diseases: A Network Approach, Moreira-Costa et al. (2021)

Neurodegenerative – exosomes in the CNS. Exosomes appear to have a relevant role in disease pathogenesis for Alzheimer's Disease (AD) and Parkinson's Disease (PD), the world's most and second-most prevalent neurodegenerative diseases, respectively. Studies suggest exosomes mediate cell communication at the central nervous system level and play important roles in maintaining normal brain physiology. The transfer of exosomes, containing specific myelin proteins, from oligodendrocytes to neurons is one example of the exosome-mediated interactions, relevant for myelination and axons survival.

Researchers have found 2 main molecules in AD pathogenesis, Aβ peptide and p-tau, with other molecular agents contributing to the spread of inflammation across the brain. Subsets of miRNA found enriched in exosomes have grown the pool of potential AD biomarkers. We expect next-generation exosome isolation methods such as EXO-NET to be positive for advancing the utility of exosomes in this high unmet need.

Exhibit 23: Exosome biomarkers for neurodegenerative disease

Biofluid	Exosome Molecules	Disease indication
Saliva	Aβ-oligomer, p-tau	Alzheimer's disease
	α-synOlig and α-synOlig/α-synTotal	Parkinson's disease
Serum	miR-135a, miR-193b, and miR-384	Alzheimer's disease
Urine	Aβ (1-42), pS396-tau, Annexin2 and Clusterin	Alzheimer's disease
	pS1292-LRRK2, LRRK2 14-3-3	Parkinson's disease

Source: The Evolving Landscape of Exosomes in Neurodegenerative Diseases, Rastogi et al. (2021)

Therapeutic applications – precision medicine potential

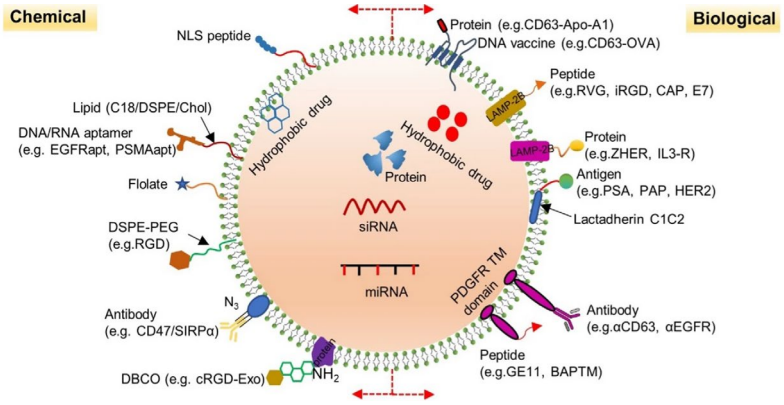
Exosomes represent a novel biological platform with distinct advantages for targeted therapy applications given their capacity for intercellular cargo delivery, high transport efficiency, low immunogenicity, and ability to target specific cells and cross the blood-brain barrier (BBB).

Development of exosome-based diagnostic disease biomarkers should accelerate as next-generation isolation technologies such as EXO-NET are introduced, providing new targets for therapeutic applications.

Exosomes-based targeted therapy. Two distinct approaches are being taken to develop exosome therapeutics:

1. using natural exosomes from producer cells (usually derived from MSCs or stem-cell progenitor derived cells) exploiting the intrinsic properties derived from the parent cells (source)
2. engineering exosomes with specific, drug like properties. This results in so called 'engineered' exosomes which have been modified either to carry a variety of payloads or modified surface membrane (see Exhibit 24) to increase targeting specificity (by modifying surface proteins) and/or as delivery vehicles for therapeutic payloads of medicinal RNAs, peptides and synthetic drugs.

Exhibit 24: Physical, biological, and chemical strategies used for surface functionalisation of exosomes



Source: Recent advances in exosome-mediated nucleic acid delivery for cancer therapy: Zhang et al (2022).

Evidence from recent studies indicates that exosomes have therapeutic potential in tumours (cancer), neurological diseases and immune diseases.

Therapeutic applications currently under investigation include the use of exosomes for targeted drug delivery, gene therapy, cancer therapy, vaccines, and tissue regeneration.

Importantly, the unique ability to cross tissue barriers, such as the blood-brain barrier, makes exosomes promising candidates for treating neurodegenerative disease and tumours in the central nervous system and the brain.

Exhibit 25: Sample of current research into the potential role of exosomes in the treatment of disease

Diseases		Therapeutic strategy
Neurodegenerative diseases	Alzheimer's disease	neprilysin quercetin miR-21, miR-29b y miR-146a
	Parkinson's disease	miR-7 miR-30a-5p
	Other neurological disorders	miR-21, miR-193b y miR-216a
Cancer	Transport of chemotherapeutics	Paclitaxel Cisplatin Doxorubicin Cancer immunotherapy
	Cancer immunotherapy	M1 macrophage-derived exosomes CAR-T cell-derived exosomes miR-139-5p miR-381
	Biological reprogrammers of cancer cells	miR-140-3p miR-5100 miR-1249, miR-126
Cardiovascular diseases	Cellular conditioning	miARN-21-5p miR-146a, miR-181b y miR-126 ßARKct-CDC exosomes
Infectious diseases	Bacterial infections	antimicrobial peptides: cathelicidin LL-37, human
	Sepsis	miR-21 super-repressor IkB CD24 and T cell-derivedexosome
	COVID-19	MSC-derived exosomes (ExoFlo®)
		Zofin™

Source: Exosomes: Potential Disease Biomarkers and New Therapeutic Targets, Mosquera-Heredia et al 2021.

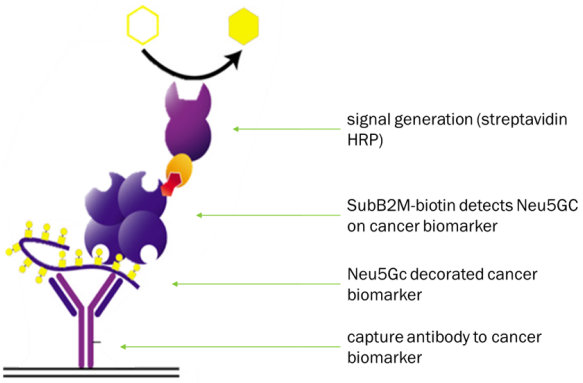
SubB2M Technology: Improving Single Cancer Biomarker Tests

How It Works: Leveraging Novel, Highly Specific Ligand to Detect Neu5Gc

The SubB2M[14] platform utilises a highly specific probe (a genetically engineered lectin[15]) developed to bind with Neu5Gc, a pan-cancer marker found in multiple human cancers. SubB2M technology was in-licensed from University of Adelaide and Griffith University in April 2020. As such, IIQ holds the exclusive worldwide rights to the SubB2M intellectual property for diagnostic applications.

Scientific rationale. Neu5Gc occurs as cells transform to malignancy resulting from aberrant glycosylation (see Appendix 1 – Glossary) caused by abnormal expression of certain enzymes involved in modifying of proteins and the regulation of cell growth and differentiation, cell adhesion, cell-to-cell communication, and immune recognition. IIQ is currently developing SubB2M-based immunoassays (ELISA) for multiple cancers, with an initial focus on the monitoring of breast and ovarian cancer.

Exhibit 26: SubB2M immunoassay

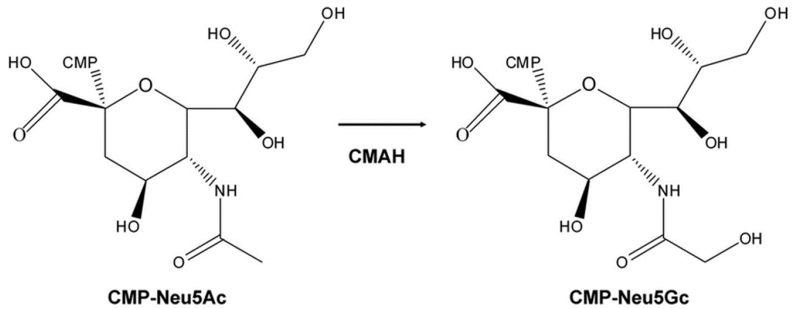


Source: INOVIQ.

The science of Neu5Gc – a novel pan-cancer biomarker

N-Glycolylneuraminic acid (Neu5Gc) is a sialic acid molecule not typically found in humans. This is due to the absence of the CMAH (CMP-Neu5Ac hydroxylase) enzyme responsible for converting the precursor to Neu5Gc in humans owing to an irreversible genetic mutation millions of years ago. Neu5Gc has been consistently found in various human epithelial cancers including breast, colon, lung, prostate, and ovarian, and as such, is a novel cancer biomarker.

Exhibit 27: Humans cannot synthesise Neu5Gc due to inactive CMP-Neu5Ac hydroxylase (CMAH) gene



Source: N-Glycolylneuraminic Acid on Human Epithelial Cells Prevents Entry of Influenza A Viruses That Possess N-Glycolylneuraminic Acid Binding Ability - Tadanobu Takahashi et al (2014).

[14] The name SubB2M derives from the second mutant version of the B-subunit of the Shiga toxigenic Escherichia coli Subtilase cytotoxin engineered to be a Neu5Gc-specific lectin.

[15] Carbohydrate-binding protein

Clinical Strategy: Combining SubB2M with FDA-Approved Cancer Biomarkers

ResearchDx – Contract Research Organisation (CRO) for LDT development of SubB2M assays (ovarian and breast cancer)

In April 2022, IIQ engaged ResearchDx, a US-based specialty CRO, to further develop and validate SubB2M-based tests. As such, the company has provided a technology transfer data package for SubB2M SPR and SubB2M/CA125 and SubB2M/CA15.3 immunoassays, which includes in-house developed CA125 and CA15.3 monoclonal antibodies and GMP-grade SubB2M protein for commercial assay development. As such, both SubB2M in ovarian and breast cancers are being developed as ELISA tests, the most used test format in commercial labs.

ResearchDx operates a CAP/CLIA certified laboratory, PacificDx, that offers state-of-the-art facilities and expertise to undertake the design, analytical and clinical validation of Laboratory Developed Tests (LDTs) within a single laboratory (including high-complexity tests). As such, ResearchDx is a potential laboratory partner for IIQ in its initial efforts to commercialise the SubB2M tests as LDTs in the USA, where the tests can be developed and validated for their intended use in the PacificDx clinical laboratory and offered to hospitals, clinicians, and doctors' offices to aid in the detection of cancer.

Ovarian cancer clinical application (2HCY23)

Exhibit 28: SubB2M for ovarian cancer: at a glance

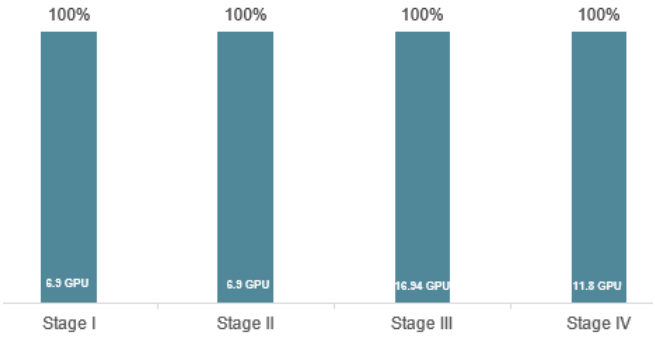
Mechanism	Detects CA125 decorated by the pan-cancer marker Neu5Gc
Development status	SubB2M-based ELISA imunoassay under development by US-based ResearchDX
Clinical area of focus	Ovarian cancer - monitoring
Next milestone	Development and analytical validation
Target launch date	2HCY23

Source: MST Access.

Rationale for incorporating CA125: There are currently no effective screening strategies for the early detection of ovarian cancer. CA125 is a blood biomarker that is commonly used to monitor ovarian cancer. However, other factors can cause CA125 to be elevated including menstruation, endometriosis and ovarian cysts. To improve the accuracy of CA125 in detecting ovarian cancer, it is important to negate the impact of non–cancer-related CA125 elevation. Since only CA125 from cancer will be decorated with Neu5Gc, a CA125-SubB2M immunoassay could be used to distinguish between tumour-derived and non-tumour-derived CA125. Therefore, it is postulated that a CA125-SubB2M immunoassay should improve the specificity and sensitivity for detection of ovarian cancer over CA125 alone.

Clinical development and clinical study results: Proof-of-concept data generated from retrospective case-control studies conducted by the Institute for Glycomics, Griffith University, showed the SubB2M-based SPR test detected ovarian cancer at 100% sensitivity and 100% specificity across all stages compared to healthy controls (n = 69).

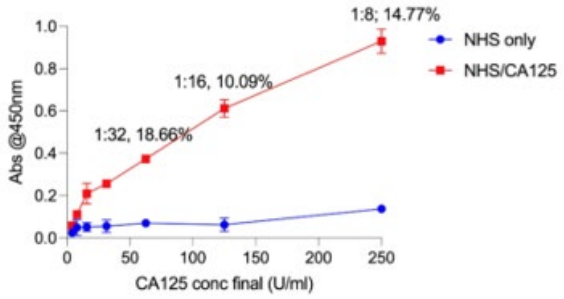
Exhibit 29: Sensitivity by stage at specified cut off GPU (Glyco Protein Units) using a SubB2M-based SPR test



Source: INOVIQ.

Griffith conducted further work including assay design, prototype development and feasibility testing of a SubB2M/CA125 ovarian cancer test. Proof-of-concept data generated showed that the CA125-SubB2M assay format could distinguish between normal human serum (NHS) and serum spiked with CA125 (NHS/CA125).

Exhibit 30: CA125-SubB2M ELISA (500ng/ml) for ovarian cancer



Source: INOVIQ. NB: NHS = Normal Human Serum.

Breast cancer clinical application (1HCY23)

Exhibit 31: SubB2M for breast cancer: at a glance

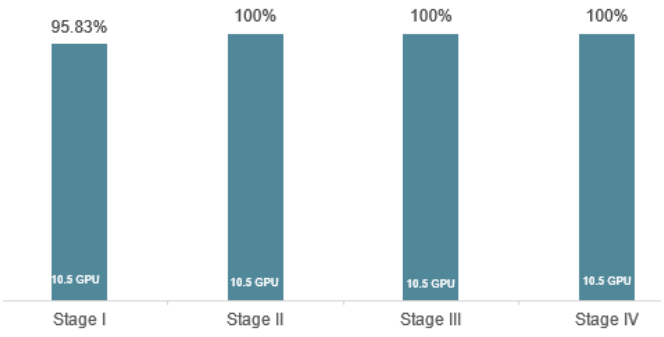
Mechanism	Detects CA15.3 decorated by the pan-cancer marker Neu5Gc
Development status	SubB2M-based ELISA imunoassay under development by US-based ResearchDX
Clinical area of focus	Breast cancer - monitoring
Next milestone	Development and analytical validation
Target launch date	1HCY23

Source: MST Access.

Rationale for incorporating CA15.3: As with CA125, non-cancerous conditions of the ovary and liver can cause CA15.3 to become elevated. As such, developing a reliable, sensitive, and accurate breast cancer test using CA15.3 required a way to mitigate the impact of non-cancer-related elevation using SubB2M. As with CA125, since only CA15.3 from cancer will be decorated with Neu5Gc, a CA125-SubB2M immunoassay could be used to distinguish between tumour-derived and non-tumour derived CA125. Griffith could detect breast cancer across all stages with 95% sensitivity and 100% specificity.

Clinical development and clinical study results: Griffith University showed the SubB2M-based SPR[16] test detected breast cancer at over 95% sensitivity and 100% specificity across all stages (n = 118).

Exhibit 32: Sensitivity by stage at 10.5 GPU cut-off using a SubB2M-based SPR test



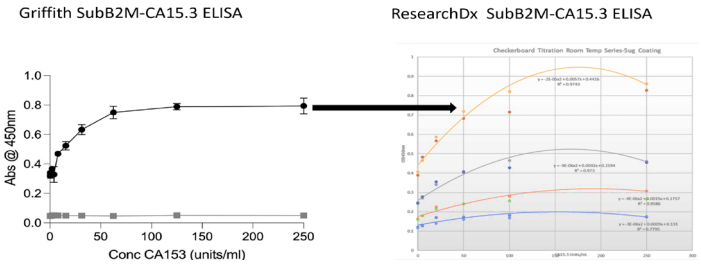
Source: INOVIQ.

Griffith conducted further work including assay design, prototype development and feasibility testing of SubB2M/CA15.3 test for breast cancer. The SubB2M/CA15.3 test has now been transferred to ResearchDx for

[16] Surface Plasmon Resonance (SPR) analysis is considered a highly sensitive technique for assessing binding kinetics and affinity as well as binding specificity between tow biomolecules (see glossary).

further development and optimisation, before entering clinical testing for monitoring BC compared to the standard CA15.3 test.

Exhibit 33: CA15.3-SubB2M assay for breast cancer- Successfully replicated by ResearchDx



Source: INOVIQ.

Pan-cancer diagnostic application (surveillance & early detection) – general health panel

Exhibit 34: SubB2M for general health panel application: at a glance

Mechanism	Detects the pan-cancer marker Neu5Gc
Development status	Currently being evaluated by INOVIQ
Clinical area of focus	Multi-cancer testing (TBD)
Next milestone	TBD
Target launch date	TBD

Source: INOVIQ.

In addition to improving the specificity of existing single cancer biomarker tests, SubB2M provides IIQ with an opportunity to develop a general test to detect the general presence of Neu5G and thereby the presence of cancer. This would use the SubB2M probe, on a standalone basis, to test for elevated Neu5Gc concentrations. As such, IIQ has indicated it may take the SubB2M pan-cancer test forward as an SPR test.

The most likely scenario in this application would see Neu5Gc used as a pan-cancer biomarker for multiple cancers in a general health panel that would require further diagnostic work-up if the test was positive (elevated Neu5Gc). Follow-up testing could include further blood tests or imaging to determine cancer type. IIQ is also evaluating a two-step SPR process to (1) identify if an individual tests positive to the pan-cancer marker Neu5Gc and (2) run a series of cancer-specific antibodies to determine the type of cancer.

Combining SubB2M with Next-Gen Surface Plasmon Resonance (SPR) for Pan-Cancer Test

Feasibility studies to date in the SubB2M program have used Surface Plasmon Resonance (SPR)–based tests, considered the gold standard in direct biomolecular interaction sensing, to directly measure the levels of the cancer biomarkers. SPR is an optical biosensor technology that uses changes in refraction of light shone onto a metallic surface to detect interactions at the molecular level. The SPR technique allows molecular interactions in a target of interest to be measured ('characterised') without the use of a fluorescent activating enzyme as used in ELISA formats.

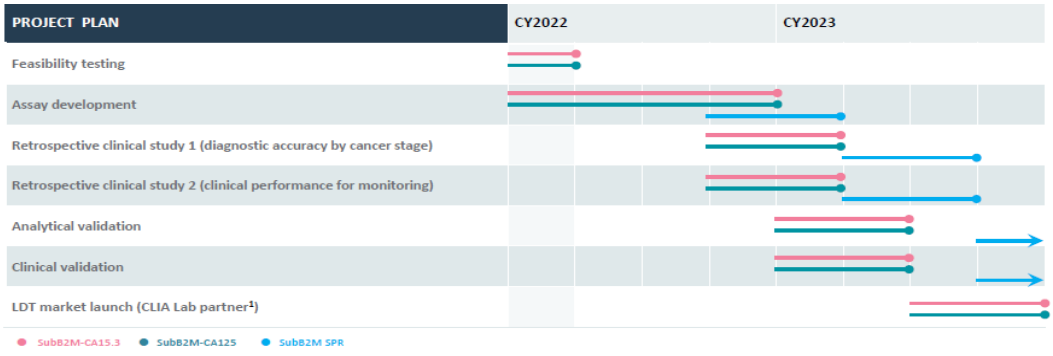
Rationale: SPR-based platforms that process a patient sample to detect and quantify biomarkers using liquid biopsies for cancer patients represent a new alternative to conventional approaches, such as cell culture methods (histopathology/cytology), enzyme-linked immunosorbent assays (ELISA), next-generation sequencing (NGS), and polymerase chain reaction (PCR)–based platforms), currently in use in commercial laboratories and considered highly efficient for processing relatively large numbers of samples[17]. Notably, the use of an SPR platform enables the measurement of multiple glycoproteins with aberrant Neu5Gc leading to improved sensitivity and specificity for cancer. Next generation SPR instruments with smaller footprint (scaled-down benchtop) versions for use in diagnostic/pathology labs could be positive for IIQ considering compelling data rendered to date and reducing the risk inherent when transferring technology to other currently widely used platforms such as ELISA.

[17] Surface Plasmon Resonance for Biomarker Detection: Advances in Non-invasive Cancer Diagnosis: Bellassai et al (2019)

Commercial Strategy (Ovarian and Breast Cancers) – Developing ELISA Assays in Partnership with ResearchDx

IIQ's near-term commercial strategy for SubB2M is to enter the market as a Laboratory Developed Test (LDT). The company has provided an indicative timeline covering all three products: SubB2M-CA15.3 (SubB2M BC – for breast cancer), SubB2M-CA125 (SubB2M OC – for ovarian cancer), and SubB2M SPR (for multi-cancer testing in a general health panel) – see Exhibit 35.

Exhibit 35:IIQ timelines for development of SubB2M products



Source: INOVIQ.

Next steps: translating promising lab results into a clinically validated product

After the discovery of a promising biomarker, IIQ has laid out the following steps to clinical validation.

Assay development: Having established assay feasibility in-house, the research-stage assay is transferred to a CRO[18] for development of a commercial assay platform – in the case of SubB2M OC and BC for monitoring recurrence, to the ELISA format (from its current SPR format). At this point, the assay components, reagents, and methods are developed and optimised to measure the biomarker/s of interest in order to achieve the required performance characteristics.

Analytical and clinical validation steps come next – these may be run in parallel.

- Analytical validation measures the analytical performance of the assay or how accurately and reliably the test measures the analyte(s) of interest in the patient specimen. Analytical validation is typically performed by assaying the same set of samples by both the assay used in the initial discovery and the clinical deployment platform to determine robustness and reproducibility of the measurements.
- Clinical validation measures the clinical performance of the test including sensitivity, specificity and utility for the clinical indication in the intended population or how accurately and reliably the test result correlates with the clinical indication or the outcome of interest.
- Retrospective clinical study 1 (diagnostic accuracy by cancer stage) – analyses samples archived from cancer patients in different stages of cancer.
- Retrospective clinical study 2 (clinical performance for monitoring) – analyses samples archived from cancer patients who have been treated and experienced a recurrence of the cancer.

LDT market launch (CLIA lab partner): IIQ will license to a laboratory partner both SubB2M OC and SubB2M BC with its laboratory partner. At this stage, the company has indicated its SubB2M Neu5Gc surveillance test will be developed on the SPR platform and offered as an LDT through a laboratory partner in an SPR format but is yet to confirm marketing plans.

Additional considerations for commercialisation include further development and clinical studies to gain regulatory approval by FDA, reimbursement, and ultimate incorporation into clinical guidelines.

[18] Contract Research Organisation

BARD1 Technology: Novel Autoantibody Technology for Ovarian and Breast Cancers

How It Works: Seeking Variations that Indicate Pathology

IIQ's proprietary BARD1 technology platform measures autoantibodies (antibodies produced by a cancer patient's immune system) to BARD1 variants encoded by the BARD1 gene which are thought to be pathogenic, and which tend to be highly expressed in breast cancer (BC) and ovarian cancer (OC). After measuring the autoantibodies to BARD1 variants, the technology uses a weighted algorithm to give a 'cancer score'. This allows the technology to help detect cancer earlier, even before symptoms are apparent.

Clinical and Commercial History

IIQ's proprietary BARD1 technology was originally developed at the Hospital University of Geneva, Switzerland. BARD1 Life Sciences Ltd (now INOVIQ) acquired the BARD1 technology in 2015 to develop technology relating to the company's original focus on lung cancer (IP licensed from Université de Genève), and the resulting technology was the basis of its IPO in 2016. The proprietary BARD1 technology includes BARD1 tumour markers, methods, and algorithms. The BARD1 autoantibody technology was transferred to the Luminex platform with Thermo Fisher Scientific to enable development of a 20-peptide multiplex assay for further development and validation.

The BARD1 (BRCA1-associated ring domain), referring to both the gene and protein, was discovered in 1996 and is closely associated with its well characterised binding partner BRCA1, whose variant gene, discovered in 1994, is commonly associated with hereditary BC and OC. BRCA1 is almost always found in the nucleus bound to BARD1 which is thought to function as a stabiliser. Interest in altered BARD1 protein as target antigens of interest followed the discovery that mutations in BRCA1 and BARD1 predispose carriers to BC and OC. It was assumed that altered BARD1 proteins would prompt an immune response in cancer patients, producing autoimmune antibodies against various epitopes of the mutated BARD1, which could then be detected as cancer biomarkers. An epitope is the part of an antigen molecule (a molecule of a substance in the body prompting an immune reaction) to which an antibody attaches itself.

The company has previously conducted research in retrospective case control studies showing accuracy of BARD1 antibody tests for detection of lung, breast, and ovarian cancers. For ovarian cancer, researchers examined 400 serum samples from both OC patients and healthy controls. They assessed how the autoantibodies in the samples reacted to 20 epitopes of BARD1 and a concentration of cancer antigen 125 (CA125). Autoantibody reactivity and CA125 were also tested for 261 plasma samples of OC with or without mutations in BRCA1/2, BARD1, or other predisposing genes, and healthy controls.

Exhibit 36: BARD1 laboratory data

Product	Study	n (cancer:normal)	AUC	Sensitivity	Specificity
BARD1 **Ovarian**	OC-CA125 (ave risk)	400 (200:200)	0.95	88%	93%
	OC- R001 (high risk)	261 (127:134)	0.97	89%	97%
BARD1 **Breast**	BC-001a (ave risk)	123 (61:64)	0.86	70%	88%
	BC-001b (benign)	110 (61:49)	0.84	85%	76%
BARD1 **Lung**	LC-POC (ave risk)	187 (94:93)	0.86	80%	77%

Source: INOVIQ.

The company is currently conducting a review of the BARD1 autoantibody program during which time no further investment is planned. This coincides with news of legal proceedings being pursued by former BARD1 executive director and Chief Scientific Officer, Dr Irmgard Irminger-Finger, against the company. The proceeding has been listed for trial in February 2023.

Commercialised Products

IIQ has two products in market: EXO-NET® (RUO) (see Research applications p.15) and the hTERT test.

hTERT ICC Assay – Anti-hTERT Antibody

Brought in through the Sienna acquisition, the hTERT test is a proprietary immunocytochemistry (ICC) assay that detects hTERT, a component of telomerase, which is upregulated in most human epithelial cancers.

The hTERT test was initially commercialised by Sienna in FY17 as an Analyte Specific Reagent (ASR), an Anti-hTERT Antibody (SCD-A7), that was sold to a CLIA pathology laboratory for development and validation of their in-house hTERT test (LDT). It was then registered as a class 1 medical device in the USA and licensed to StatLab (a specialty urological reagents distributor).

The product is registered in the US (FDA Class I), Europe (CE-IVD mark), South Korea (MFDS Class II), and Australia (TGA Class II).The hTERT test is currently sold in the USA and being introduced in South Korea, Israel, Greece and Sweden.

The hTERT test is sold as an adjunct to urine cytology testing to assist in the diagnosis of bladder cancer, the standard non-invasive test performed on urine samples being examined for the presence of cancerous cells (bladder cancer).

hTERT is currently sold in the USA and is being introduced in South Korea, Israel, Greece and Sweden.

Exhibit 37: hTERT registration

Jurisdiction	Registration details
USA (FDA)	Class 1 Medical Device in the USA with existing reimbursement in that market
EUROPE (CE MARK)	CE MARK classed as 'General' Medical Device
AUSTRALIA (TGA)	Class II Medical Device
South Korea	Class 2 IVD in South Korea

Source: INOVIQ.

Clinical use – confirmatory testing of atypical/inconclusive results in bladder cancer

Cytology is typically used to diagnose high-grade urothelial carcinoma, the most common type of bladder cancer in the United States. However, cytology cases result in atypical/equivocal or inconclusive results in 1 out of 4 patients. With no clear consensus, or standardisation around protocols for atypical results, this can lead to either missing early cancer diagnoses or unnecessary invasive tests such as cystoscopy and tissue biopsies.

The hTERT test provides information that categorises atypical results as low or high risk. As such, it provides additional and confirmatory information to assist in the diagnostic assessment of bladder cancer. The product is compatible with all major industry standard liquid-based cytology preparations such as ThinPrep®.

Regulatory Pathway – Key Considerations

United States

The regulatory process in the United States has multiple pathways. FDA approval/ clearance, which is the gateway to broader commercialisation, involves risk-based classification, which in turn defines levels of claims allowed for marketing purposes. The classification of IIQ's devices (as with all products) will be determined with reference to:

- the intended diagnostic indication (test for cancer etc)
- the level of risk posed by the device (determined as harm caused by missed diagnosis, overdiagnosis and false positives)
- test type or use targeted along the diagnostic continuum (screening, diagnosing, monitoring).

Exhibit 38: FDA clearance and classification of medical devices (including IVD products) – marketing claims reflect levels of risk

Classification of Medical Devices	Details
Class I	Simple devices posing no or minimal risk to the user and exempt from FDA clearance. These are about 40% of all devices.
Class II	Moderate risk to the user and generally require FDA clearance before getting marketed and accounts for about 50% of all devices. This is the 510k pathway for mod-risk devices with a predicate device. Can also be De Novo application for mod-risk device with no predicate, requires clinical validation.
Class III	These life- supporting or life-sustaining devices pose a serious risk to the user and require a PMA and FDA clearance before marketed. This is the PMA process for novel high-risk devices

Source: https://juniperpublishers.com/ctoij/CTOIJ.MS.ID.555586.php; www.fda.gov/medical-devices/ivd-regulatory-assistance

Notwithstanding regulatory approval, payor reimbursement of the test will be a key driver to support the sale of the test. IIQ's stated near-term commercial strategy relies on the successful development and launch of its SubB2M tests for monitoring of OC and BC respectively as laboratory developed tests, or LDTs, in the first instance. Notably, these tests are improvements on the approved CA125 and CA15.3 tests, which have US FDA regulatory approval and reimbursement.

Laboratory-Developed Tests (LDTs) – faster route to market

Laboratory-developed tests (LDTs), also known as 'in-house' or 'home brew' tests, are defined by the FDA as IVDs that are (1) intended for clinical use and (2) designed, manufactured, and used within a single laboratory.[19]

LDTs are a subset of IVD devices regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA) regulations. Historically, the LDT pathway has provided a faster route to market. IIQ is pursuing an LDT route as the fastest path to generating revenues and introducing the tests to physicians. As such, the LDT route will evaluate initial market acceptance by clinical adoption and enable real-world data and biobank of samples for future larger-scale clinical trials.

Exhibit 39: FDA-approved pathways such as 510 (k) or PMA (left) vs. the CMS-regulated LDT pathway (right)

	FDA	CMS
Primary statutory authority	Food, Drug, and Cosmetic Act, as amended by the Medical Device Amendments of 1976	Public Health Services Act, as amended by the Clinical Laboratory Improvement Amendments (CLIA) of 1988
Oversight	All IVDs (including LDTs and reagents) are categorized as medical devices, but FDA has historically not exercised its regulatory authority with respect to LDTs.	Labs conducting tests on human samples. Inspectors evaluate the qualifications of lab personnel and testing processes and review their analytical validation processes for all tests, whether LDT or IVD.
Validation requirements	Analytical validity Clinical validity	Analytical validity
How are tests validated?	Through premarket review, manufacturers of moderate- and high-risk IVDs must establish that a test detects or measures the intended analyte with appropriate precision and accuracy. Human studies are typically required to demonstrate the test's ability to predict a disease or condition as intended.	Labs performing tests that are not subject to FDA clearance or approval must establish performance characteristics of that test ("an analysis of accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference interval").
When are tests reviewed?	At various points before the legal marketing of that test.	During inspections every two years (may be up to two years after an LDT is first performed).
Adverse event reporting	Mandatory reporting of adverse events by manufacturers, device user facilities (hospitals, nursing homes, etc.), and importers. Providers and patients may also voluntarily report serious adverse events.*	Not required. No mechanism exists to collect such information.
Recall authority?	Yes	No
	CMS = Centers for Medicare & Medicaid Services FDA= U.S. Food and Drug Administration,	

Source: The Role of Lab-Developed Tests in the In Vitro Diagnostics Market (The PEW Charitable Trusts, October 2021).

[19] Single laboratory refers to a facility with a single CLIA (Clinical Laboratory Improvement Amendments) certificate

Next steps: FDA 510(k)/PMA/De Novo pathways – required for marketing to commercial labs

IIQ's longer-term strategy of expanding the commercial availability of its tests will require formal FDA regulatory approval. The plan to expand the marketing authorisation will require FDA clearance via a 510(k), or in the absence of a predicate device, De Novo or PMA approval. As such, the test may then be made commercially available for sale to any CLIA-accredited, US-based pathology laboratory.

510 (k): A 510 (k) clearance is not an approval. The manufacturer of the medical device must demonstrate that the device is substantially equivalent to a predicate device that has been previously FDA cleared. Diagnostics approved via this pathway are classified as Class II tests and allow claims for use. A 510(k) could require a clinical trial, but smaller than those needed for a De Novo or PMA designation. In the case of SubB2M, if combined with the current standards of care (CA125, CA15.3), IIQ could use these as predicates. Adding a 510 (k) clearance to a staged rollout would expand sales of tests beyond the single CLIA-certified lab to all commercial labs.

De Novo and PMA: The De Novo Classification Process provides a path to market for a novel device for which general or general and special controls are adequate to reasonably assure safety and effectiveness for its intended use, but for which there is no legally marketed predicate device. In addition to providing marketing authorisation, this process classifies the device into Class I or II and creates a new classification regulation, and the device may be used as a predicate device for future 510 (k) submissions as appropriate.

Cancer diagnostic tests are most likely be designated Class III, although a lower rating may be sought based on a reduced scope of claim for intended use. This could reflect the level of sensitivity or specificity required and whether intended use refers to screening, diagnosis, or monitoring (NB. screening use is higher risk classification than monitoring use). Regulatory advice will be sought prior to deciding on the proposed course (De Novo or PMA). For the more rigorous PMA designation, and subject to FDA guidance, IIQ would have to conduct sizeable clinical trials.

European Union

In the EU, IVD devices are regulated under the new In Vitro Diagnostic Medical Devices Regulation (2017/746/EU) (IVDR), which is a risk-based classification system replacing the former, less stringent European IVD Directive.

Exhibit 40: European framework for In Vitro Diagnostic Medical Devices Regulation classification

Class	Individual risk	Public health risk
A	Low	Low
B	Moderate	Low
C	High	Moderate
D	High	High

Source: https://ec.europa.eu/commission/presscorner/detail/en/ip_21_6965.

Competitive Landscape – Cancer Diagnostics Market

IIQ's broad portfolio of cancer-focused diagnostic programs provides the company with multiple opportunities to improve on current standards of care and/or participate in the emerging role of liquid biopsy approaches in cancer. As such, these can be classified both by type of cancer being targeted (e.g., ovarian, breast, pan-cancer) and use (screening, diagnostics, selection, monitoring) or by the enabling technology platform (e.g., exosome capture) used in the process of detection.

Competition by Cancer Type

Ovarian cancer – currently no approved tests for ovarian cancer screening

There are currently no approved tests for ovarian cancer screening in the market due to insufficient sensitivity and specificity for detecting early-stage cancer. Further, progress in development of non-invasive options for detecting and monitoring ovarian cancer has been slow. Consequently, the unmet need for a non-invasive, accurate and reliable test for early detection of ovarian cancer represents a large market opportunity. As such, screening for ovarian cancer is an attractive target for the company's first EXO-NET collaboration with UQ. Similarly, improving on the low sensitivity and limited specificity of single cancer markers like CA125 makes ovarian cancer monitoring a natural target for IIQ's SubB2M test.

Imaging using transvaginal ultrasound (TVU), with and without laboratory tests, is still the mainstay in early ovarian cancer detection. Beyond the use of CA125 and TVU scans to assess patients with suspected ovarian cancer, the choices available and therefore the competitive landscape remains thin. Alternative methods such as ROMA scores do offer a combination approach to measure established biomarkers, as adjuncts to imaging, but the unmet need in screening, diagnosis and monitoring remains high.

Exhibit 41: Ovarian cancer blood tests with FDA clearance

Company	Diagnostic Test	Clinical Application	Markers /Details	Sensitivity	Specificity
Generic	CA 125	Monitoring	CA 125	50-73.9%	80.0%
Generic	HE4	Monitoring	HE4 (human epididymis protein 4)	72.9%	95.0%
Fujirebio Diagnostics	ROMA®	Diagnostic	Combines measures of HE4, CA 125 and menopausal status and complements independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.	80.9%	74.9%
Vermillion/Aspira Labs	OVA1®	Diagnostic	Combines 5 biomarkers(CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, transferrin), NGS/Liquid biopsy, The test is currently approved for use as an adjunct to physical examination and imaging and produces a risk assessment score within the range of 0-10.	92.4%	53.5%
Vermillion/Aspira Labs	Overa®	Diagnostic	Next-generation of OVA1® test Combined 5 biomarkers (CA 125, apolipoprotein A-1, transferrin, follicle-stimulating hormone, HE4), NGS/Liquid biopsy	92.0%	69.0%

Source: Current and Emerging Methods for Ovarian Cancer Screening and Diagnostics: A Comprehensive Review; Liberto et al (2022).

Overall, research in ovarian cancer diagnostics is expanding with multi-omics approaches, increasing power of machine learning algorithms, and the increasing focus on new cancer biomarker types, such as miRNA, EVs, autoantibodies, the cancer microbiome and metabolomics.

Exhibit 42: Ovarian cancer diagnostics research – emerging technologies and cancer biomarker types

Test Name	Markers	Modality	Potential Clinical Application(s)
OCaMIR	miR-182, miR-183, miR-202, miR-205, miR-508, miR-509-3, miR-513B, and miR-513C	MicroRNA	Diagnostic/Prognostic
N/A	microbial derived EVs.with serum CA125 and age	Exosomal	Diagnostic
N/A	HSF1, CCDC155, and serum CA125	Autoantibodies	Diagnostic
N/A	urinary biomarkers: Acetone, Allantoin and others	Metabolite	Diagnostic

Source: Current and Emerging Methods for Ovarian Cancer Screening and Diagnostics: A Comprehensive Review; Liberto et al (2022).

Breast cancer – only a slightly more crowded landscape; ample room for new entrants

Similarly, the competitive landscape in early-stage breast cancer diagnostics, although slightly more crowded than ovarian, offers average levels of sensitivity and specificity.

Exhibit 43: Breast cancer diagnostic blood tests

Company	Diagnostic Test	Clinical Application	Markers /Details	Sensitivity	Specificity
Generic	CA 15-3	Monitoring	CA 15-3	75-76.9%	85-93%
Generic	CA 27.29	Monitoring	CA 27.29 assay cannot detect all breast cancers	75.0%	77.0%
Provista Diagnostics	Videssa®	Diagnostic	Combines serum protein biomarkers with tumor associated autoantibodies. Used as an adjunct to imaging.	87%-92%	~85%
Myriad	BRACAnalysis CDx®	Prognostic	Prediction of therapeutic response - Companion diagnostic used in patient management related to treatment by PARP inhibitors	NR	NR
Genetic Technologies	Genetype for Breast Cancer	Predictive	Uses genetic mutations and other non-genetic clinical makers for risk assessment	NR	NR
Exact Sciences	Oncotype DX®	Predictive	21 gene assay used to predict the risk of disease recurrence in estrogen receptor (ER)-positive, HER2-negative breast cancer patients with axillary lymph node-negative or micrometastatic disease.	93.0%	94.0%

Source: Various company websites

The development pipeline remains thin and focused on screening.

Exhibit 44: Breast cancer diagnostic blood tests in development

Company	Diagnostic Test	Clinical Application	Markers /Details	Sensitivity	Specificity
BCAL	BCAL test	Screening	Developing test based on analysis of lipids derived from extracellular vesicles.	NR	NR

Source: BCAL.

Pan-cancer early detection blood-based liquid biopsies – activity stepping up

SubB2M technology with Neu5Gc used as a surrogate biomarker for simultaneous detection of multiple cancers presents a novel opportunity for the company to develop a multi-cancer screening test. An ideal multi-cancer early detection (MCED) blood-based test would also accurately predict the tissue of origin and complement existing screening approaches which are limited to a handful of individual cancers. The competitive landscape for MCED blood tests is expanding given improving biomarker analysis supported by new machine learning and multi-omic approaches. Exhibit 45 highlights the current leaders in the space.

Exhibit 45: Multi-cancer or pan-cancer early detection blood-based liquid biopsies – key players

Company	Cancer application(s)	Product name	# Cancers	Technology	Product status
20/20 GeneSystems	Multicancer screening	OneTest™	6	Six cancer biomarker tests, personal health data with an AI algorithm	On market
Burning Rock	Multicancer screening	Burning Rock ELSA-Seq	12	Deep methylation sequencing	in development
Delfi Diagnostics	Multicancer screening	DELFI-L101	N/A	cfDNA whole-genome NGS followed by fragmentation analysis	in development
Exact Science	Multicancer screening	Multi-cancer early detection (formerly CancerSEEK)	16	Multiplex amplicon sequencing + proteomic biomarker detection	in development
Grail	Multicancer screening	Galleri™	>50	>100,000 differentially methylated regions of cfDNA, predicts tissue of origin	On market
Inivata	Tumor mutation profiling	InVisionSeq™	N/A	Tumor mutation profiling	On market
Singlera Genomics	Multicancer screening	PanSeer	5	477 differentially methylated regions	For research use only

Source: Transforming the landscape of early cancer detection using blood tests—*British Journal of Cancer* (2021), Using all our genomes: Blood-based liquid biopsies for the early detection of cancer: Adams et al (2021), company websites.

Competition by Enabling Technology – Exosome Capture

Exosome diagnostic companies – also represent commercial opportunity

EXO-NET's competitive advantage in isolating exosomes provides the basis or a potentially more effective cancer research tools, diagnostic and therapeutic.

As such, we consider EXO-NET an enabling technology and list the key players in the exosome space to highlight the breadth of applications and potential commercial opportunities available given the overwhelming number of emerging players with projects in development stage. The landscape is dominated by both Thermo Fisher Scientific and Qiagen, as providers of technologies to the research sector, but also in the number of partnering agreements established with smaller players.

Exhibit 46: Exosome diagnostic companies

Company Name	Application/Mkt Segment	Focus	Clinically Phase
Aegle Therapeutics	Therapeutic	Rare skin disease	In Development
Anjarium Biosciences	Diagnostic/Therapeutic	Hybridosome™ technology	In Development
Biological Dynamics	Diagnostic	Early-Stage Multi-Cancer Detection	In Development
BioTechne	Diagnostic	Mulitple including EV isolation method developed in-house by Exosome Dx (acquired by Biotechne)	On market
Capricor Therapeutics	Therapeutic	Regenerative medicine.	In Development
Caris Life Sciences	Diagnostic	Breast Cancer detection	In Development
Clara Biotech	Diagnostic	Early cancer detection; Alzheimer's Disease; Virus Detection	In Development
Codiak Biosciences	Therapeutic	Exosomes as drug delivery	In Development
EV Therapeutics Inc.	Therapeutic	Enhancing immunotherapy efficacy in colorectal cancers	In Development
Evox Therapeutics	Therapeutic	Wide range of disease areas	In Development
Exogenus Therapeutics	Therapeutic	Exosome-based therapeutics for skin lesions	In Development
Exopharm	Therapeutic	Exosome purification processes	In Development
Exopharm Pty Ltd	Therapeutic	Drug delivery	In Development
Exosome Sciences (subsidiary of Aethlor	Diagnostic	Exosome-based biomarkers to diagnose and monitor neurological disease and related conditions	In Development
MDimune Inc	Therapeutic	Drug delivery	In Development
Mir Scientific	Diagnostic	Bladder and prostate cancer patient trials ongoing.	In Development
Organicell	Therapeutic	Tissue repair	In Development
Qiagen	Research	A leading global provider of sample and assay technologies for molecular diagnostics, applied testing, academic and pharmaceutical research.	N/A
ReNeuron	Therapeutic	Allogeneneic therapies using CTX neural stem cells	In Development
Thermo Fisher Scientific	Research	A leading global supplier of scientific instrumentation, reagents and consumables, and software services.	N/A
VivaZome Therapeutics Pty Ltd	Therapeutic	Treatments for debilitating and/or life-threatening disorders	In Development

Source: Various including exosome-rna.com, bioinformant.

Intellectual Property

IIQ has a broad patent portfolio protecting its core biomarker isolation and detection technologies and products. All its intellectual property is either owned or exclusively licensed.

The company has 42 granted patents, 14 pending and 2 international (PCT) applications, as of 26 July 2022.

IIQ has IP protection across key jurisdictions (including US, Europe, Asia and Australia).

IIQ has registered trademarks for INOVIQ® and EXO-NET®.

Exhibit 47: IIQ's patent portfolio as of 26 July 2022

Patent Family	Title	Granted	Pending	Expiry
SubB2M				
PCT/AU2017/051230 (WO2018/085888)	Subtilase cytotoxin B subunit mutant	AU, US	BR, CA, CN, EP, IN, JP, KR, US(cont)	2037 US 2038
PCT/AU2022/050470 (Application not yet published)	Methods of analysing a sample			2042
BARD1				
PCT/FR01/02731 (WO2002/018536)	Truncated BARD1 protein, and its diagnostic and therapeutic uses	US		2024
PCT/IB2011/053635 (WO2012/023112)	BARD1 isoforms in lung and colorectal	AU, BR, CA, CN, CN(div), EP, HK, IL, JP, JP(div), SG, US, US(cont)		2031 US(cont) 2032
PCT/IB2011/054194 (WO2012/038932)	Kits for detecting breast or ovarian cancer in a body fluid sample and use thereof	EP, US, US(cont)		2031 US and US(cont) 2032
PCT/EP2014/073834 (WO2015/067666)	Lung cancer diagnosis	AU, CN, IL, JP, SG, KR, US	CA, EP, HK	2034 US 2035
EP14002398.7	Non-coding RNA as diagnostic marker and treatment target	US		2035
hTERT				
PCT/AU2015/050060 (WO2015/120523)	Method of resolving inconclusive cytology to detect cancer	AU, CN, EP, IL, JP, US US(cont)		2035
PCT/AU2016/050764 (WO2017/027928)	Method of detecting cancer in morphologically normal cells	JP	US	2036
Molecular NETs				
PCT/US2010/058086 (WO2011/066449)	Devices for detection of analytes	CN, US(cont1), US cont2), US(cont3)	US(cont5)	2030 US(cont1) 2033 US(cont2&3) 2031
PCT/US2013/049779 (WO2014/011673)	Molecular nets	EP		2033
PCT/US2014/029823 (WO2014/153262)	Molecular nets on solid phases	AU, CN	CA	2034
PCT/AU2022/050428 (Application not yet published)	Methods relating to tumour-derived extracellular vesicles			2042

Source: INOVIQ. Cont = continuation, div = divisional. More information on country/region codes for patent jurisdictions available at https://www.wipo.int/ip-development/en/agenda/flexibilities/glossary.html.

Financials

Cash position: IIQ reported cash of A$15.4m as at end of June 2022. We view this as adequate given it represents a cash runway of 9 quarters based on the most recent quarterly reported cash outflow of A$1.7m.

Research and development: We expect R&D spend will increase significantly over the next 12 months as the company moves SubB2M programs into clinical validation. We forecast ~ A$5m for FY23 and FY24, respectively. Our modelling assumes that a 43.5% R&D tax refund in the following fiscal year will apply to these outgoings.

Revenue: Our revenue forecasts for FY23–FY25 include forecasts of contributions from both products in market (hTERT, EXO-NET® RUO) and expected revenues generated by the launch of SubB2M monitoring tests for both ovarian and breast cancers.

Valuation

We value IIQ at A$194m or A$2.11 per share (undiluted), using a risk-adjusted net present value (rNPV) method to discount future cash flows through to 2043, consistent with the expiry life of current patent families. There are 9.3m options outstanding, exercisable at various prices. As such, our fair value of the shares on a fully diluted (101.4m shares) basis is A$1.92. This represents clear upside to IIQ's A$52m market capitalisation and A$0.57 share price.

Our valuation uses a sum-of-the-parts approach, given the company's mix of assets, to arrive at a total rNPV of products (hTert and EXO-NET RUO) and development programs - SubB2M (Ovarian Cancer), SubB2M (Breast Cancer), and Exosome Ovarian Cancer screening test (collaboration with UQ) - of A$179m and net cash of A$15.3m as of 30 June 2022.

The breakdown of our rNPV model, which includes a 12.5% discount rate, is shown in Exhibit 48. Note we assume an exchange rate of US$0.73/A$1.

Exhibit 48: rNPV breakdown for IIQ valuation

Technology platform	Indication	Application	Launch (CY)	NPV (US$m)	Probability of success	rNPV (A$m)
SubB2M	Ovarian Cancer	Monitoring	2023 (LDT)	33,713,397	20%	9
SubB2M	Breast Cancer	Monitoring	2023 (LDT)	68,568,332	20%	19
EXO-NET DX (Clinical)	Ovarian Cancer	Screening	2027 (LDT), 2030 (IVD)	914,661,615	12%	145
EXO-NET Research Use Only	Various	RUO	On market	63,833,666	100%	87
hTert	Bladder cancer	Adjunct test	On market			3
Other Income (R&D tax credits)						16
Operating expenses FY22-FY36						-101
					Cash on hand	15
					Total	194
					Shares on Issue (m)	92.0
					rNPV per share (A$)	2.11
					Options (m)	9.3

Source: MST Access.

The main value driver for IIQ, in our opinion, is the collaboration with UQ on the exosome-based screening test for ovarian cancer. We have assumed this program will result in the launch of an LDT in 2027, at which point the company will out-licence to a major diagnostic partner who will assume all subsequent costs for ultimate FDA approval under a 510(k) pathway. We assume an upfront payment of US$30m in 2027, based on recent exosome licencing deals, albeit in the therapeutic space (see Exhibit 49), and 12% royalty stream paid to IIQ from 2027 onwards.

Exhibit 49: Licensing deals – exosome therapeutics

Company	Partner/Collaborator	Date	Indication(s)	Upfront (US$)	Upon commercialisation (US$)
Capricor	Nippon Shinyaku	Jan-22	Duchenne muscular dystrophy (DMD). Exosomes secreted by CAP-1002 shown to reduce oxidative stress, inflammation, fibrosis, and increase myocyte generation, as well as improve motor and cardiac function.	$30m	$705m
Carmine Therapeutics	Takeda	Jun-20	Non-viral gene therapies using red blood cell extracellular vesicles (RBCEVs).	ND	$900m
ReNeuron	Undisclosed	Apr-20	Proprietary exosomes for the delivery of novel gene silencing therapeutics.	ND	ND
Evox	Eli Lilly	Jun-20	Neurological disease targets. Exosome engineering to achieve brain/CNS-targeting, drug loading and analytics.	$20m	$ 1.2b
Evox	Takeda	Mar-20	Five novel protein replacement and mRNA therapies in rare diseases	$44m	$882m
Codiak	Sarepta	Jun-20	Five rare neuromuscular targets	$72.5m	ND
Codiak	Jazz Pharmaceuticals	Jan-19	Five classes of cancer therapies	$56m	$200m per target

Source: MST Access. ND: Not disclosed.

Near-term catalysts to our valuation are the launch of both SubB2M (Ovarian and Breast Cancer) monitoring tests and growth of EXO-NET (Research Use Only) in clinical settings.

Key assumptions of our valuation are outlined in Exhibit 50.

Exhibit 50: Key valuation assumptions

Technology platform	Metrics	Assumptions
SubB2M		
Ovarian Cancer (Monitoring)	Target population	US market in 2020: Incidence (23,820) and Prevalence (72,013)
	Pricing	US$150 per test
	Number of tests per patient p.a.	4x treatment monitoring (new cases = incidence); plus 1 x recurrence monitoring (prevalence)
	Timelines	CY23 launch as an LDT
SubB2M		
Breast Cancer (Monitoring)	Target population	US market in 2020: Incidence (253,465) and Prevalence (1,070,703)
	Pricing	US$150 per test
	Number of tests per patient p.a.	4x treatment monitoring (new cases = incidence); plus 1 x recurrence monitoring (prevalence)
	Timelines	CY23 launch as an LDT
EXO-NET DX (Clinical)		
Ovarian Cancer (Screening)	Target population	US market: Women aged 50 -74 years
	Pricing	US$750 per test
	Number of tests per patient p.a.	One test per year
	Timelines	Assuming launch as LDT in CY2027, then outlicensed to major development partner for development of IVD and launch by 2030
	Licensing	Upfront payment of US$30m in 2027 with ongoing royalty stream of 12%
EXO-NET Research Use Only		
Research Use Only	Target population	Researchers involved in EV-applied and clinical research (US, EU, Asia Pacific)
	Pricing	US$1950 per vial (List Price)
	Market size	Global exosome research market valued at US$144 million in 2021 and is expected to reach US$661 million by 2026 (Markets & Markets, 2022. Exosome Research Market - Global Forecast to 2026.)
	Timelines	On market
hTert		
Bladder cancer (Adjunct diagnostic)	Target population	US market in 2020: Incidence (80,617) and Prevalence (269,259); Used as an adjunct test in urine cytology for heamaturia patients when standard test is inconcusive, ~25% of cases.
	Pricing	US$112 per test (reimbursed under CMS - CPT code : 88342)
	Number of tests per patient p.a.	1 test per patient
	Timelines	On market

Source: MST Access.

Sources of potential upside to our valuation

Our use of rNPV analysis to value IIQ assumes:

- both SubB2M monitoring tests are commercialised as LDTs only and for the US market only
- revenues generated over the life of relevant patents
- IP generated by EXO-NET/OCRF-7 ovarian test collaboration with UQ results patent expiry in 2043
- EXO-NET® RUO is commercialised globally

As such, expansion into other markets, indications or progression of the preclinical pipeline is not included at this stage but represents significant potential upside. Similarly, acceleration of current timelines with a breakthrough designation for the EXO-NET/OCRF-7 ovarian test would likely represent valuation upside.

Sensitivities and Risks – Efficacy and Regulation Are Key

Demonstrating **efficacy in detection** of specified cancer and meeting **requirements of regulatory authorities** across different markets represent the two key risks for IIQ. Others are detailed below.

Technology Transfer

The success of IIQ's development programs rely on both the validation of the underlying mechanism of action/target of interest and the development of test formats (SPR, immunoassay) for measuring these targets. The development of various testing formats brings into question choice of reagents, antibodies other laboratory tools. This in effect represents a risk related both to technology and its transfer across testing formats.

Funding

In the absence of a development partner and with A$17.3m in cash (as at 31 March 2022), the potential need for funding remains high. Adding to funding requirements will be the choice of regulatory pathway (LDT, 510 (k), IDE) which in turn may require additional clinical trials to be conducted.

Competition

Targeting earlier detection of cancer remains an area of strong clinical interest and research development. Nonetheless, specific ovarian and breast cancers lack an early detection standard which suggests there is room for new entrants.

Development and Commercialisation

New product development of IVDs rely on the translation of promising clinical data to date to testing formats that can be validated in retrospective trials using large blood sample banks (such as the UK ovarian cancer biobank). Further, for commercialisation of the tests IIQ will need to demonstrate the benefits of adding to current standards. Central to commercialisation of the test will be the development of ELISA formats which are typically low-cost and commonly used in industry.

Regulatory Approval

Regulatory oversight of diagnostic tests Is fragmented. There are multiple frameworks under which diagnostic tests can seek regulatory approval.

As such the risks will be dependent on whether IIQ seeks FDA clearance or approval or alternatively under CLIA regulations enter the market as a LDT developed test. Notably, all IVDs (including LDTs and reagents) are categorised as medical devices, but the FDA has historically not exercised its regulatory authority with respect to LDTs. While the regulation of LDTs comes under CLIA regulation, the FDA has been pursuing control over LDTs for more than a decade, citing concerns over the level of rigour in validation and resultant safety in use.

Reimbursement

Reimbursement of the test may be a key determinant of its adoption and ultimate commercial success. This will be determined by ultimate cost and efficacy relative to current options.

Intellectual Property

A solid patent position represents a significant barrier to entry in medical technology. IIQ's current patent portfolio is expanding but is currently heavily skewed towards BARD1.

Board and Management

Dr Geoff Cumming B Sc (Hon), PhD, MBA, MAICD – Non-Executive Chairman. Dr Cumming has held senior roles in the global healthcare and biotechnology sector for more than 20 years including those of: Managing Director, Roche Diagnostic Systems (Oceania) and Managing Director/CEO of Biosceptre International Ltd. Dr Cumming was successful in securing key funding arrangements through a range of capital-raising initiatives, including large government grants, partnering and co-development deals. His most recent executive role was as Managing Director/CEO of Anteo Diagnostics Ltd (ASX: ADO). He is currently a Non-Executive Director of AnteoTech Ltd and was previously Chairman of Sienna Cancer Diagnostics Ltd (ASX: SDX) and a Non-Executive Director of Medical Australia Ltd (ASX: MLA).

Max Johnston – Non-Executive Director. Mr Johnston held the position of President and Chief Executive Officer of Johnson & Johnson Pacific. Prior to joining Johnson & Johnson, Mr Johnston's career also included senior roles with Diageo and Unilever in Australia, Africa and Europe. Mr Johnston has also held several prominent industry roles as a past President of ACCORD Australasia Limited, a former Vice Chairman of the Australian Food and Grocery Council and a former member of the board of the Australian Skills Management Institute (ASMI).

Philip Powell, BCom (Hons) ACA MAICD – Non-Executive Director. Mr Powell is a Chartered Accountant with extensive experience in investment banking, specialising in capital raisings, initial public offerings, mergers and acquisitions and other successful corporate finance assignments across a diverse range of sectors including pharma, utilities, IT, financial services, food and agriculture. He spent 10 years in senior financial roles at OAMPS Ltd, a former ASX-listed financial services group, and 10 years in audit with Arthur Andersen & Co in Melbourne, Sydney and Los Angeles.

Prof Allan Cripps, AO PhD BSc (Hons) FAHSM FASM FAIMS FIBMS FCHSM – Non-Executive Director. Prof Cripps is a distinguished academic, clinical scientist and health services leader, having made significant contributions in immunology, diagnostics and health services delivery. From 2005 to 2016, he was the Pro Vice Chancellor (Health) at Griffith University, Queensland, where he was until recently a research professor. Queensland. He had 20 years' experience in the pharmaceutical industries before becoming a full-time academic, focusing his research on mucosal immunology, respiratory tract infections, vaccine development and diagnostics.

Dr Leearne Hinch, BSc BVMS MBA – Chief Executive Officer. Dr Hinch joined INOVIQ as CEO in 2016 bringing over 20 years' experience in the life sciences industry. She has held past leadership roles as a biotechnology executive and life sciences consultant at private and ASX-listed companies including Ingeneus Solutions, Eustralis Pharmaceuticals, OBJ and Holista Colltech, where she gained a track record leading all aspects of life sciences businesses including technical, operational, and strategic. Dr Hinch has spearheaded the development of corporate strategy and partnerships, M&A transactions and capital raisings, and delivered business growth and revenue targets. She has also led development and commercialisation teams for multiple diagnostic, device, therapeutic and animal health products. Dr Hinch holds a Bachelor of Science, Bachelor of Veterinary Medicine and Surgery and a Master of Business Administration.

Dr Gregory Rice, PhD BSc (Hon) MHA Grad Dip Mgt – Chief Scientific Officer. Dr Rice is an internationally recognised academic and commercial scientist with over 30 years' expertise and experience in oncology, perinatology, exosome-based research, clinical translational research, IVD development and commercialisation. He has held numerous academic leadership positions including at the University of Queensland (UQ), Baker Heart and Diabetes Institute, University of Melbourne, and Monash University. As Director of the UQ Centre for Clinical Diagnostics (CCD), he established an exosome research facility to evaluate the clinical utility of extracellular vesicles as liquid biopsies, IVDs and therapeutics and was a Founding Director/CSO of diagnostics company HealthLinx Ltd and more recently CEO of Pregnostica SpA.

Tony Di Pietro, B Comm CA AGIA MAICD – Chief Financial Officer & Company Secretary. Mr Di Pietro is a Chartered Accountant with significant corporate accounting experience, gained both in Australia and the UK. He holds a Graduate Diploma of Applied Corporate Governance from the Governance Institute of Australia and is a member of the Australian Institute of Company Directors. Mr Di Pietro has held senior roles in the biotechnology/medtech industry for the past 15 years, including at Sienna Cancer Diagnostics.

Appendix 1 – Glossary

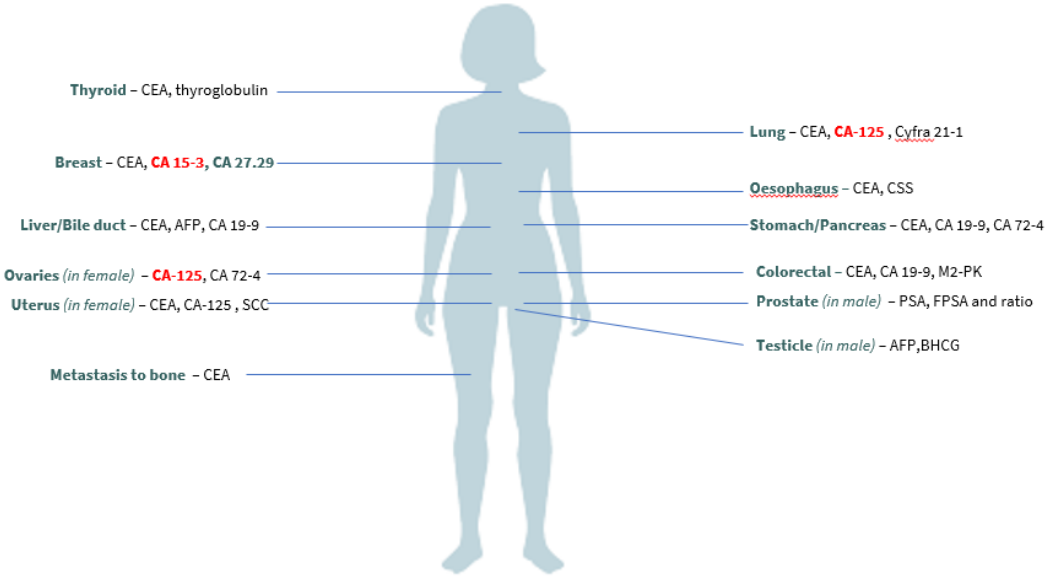
Exhibit 51: Glossary

Term	Details
Aberrant glycosylation	Glycosylation is a tightly regulated enzymatic process requiring several hundred of different, individual enzymes that modify proteins and regulate key biological functions. Aberrant glycosolation is associated with differential expressions of enzymes, such a glycosyltransferase and glycosidases, and is a hallmark of cancer playing a fundamental role in tumour development and progression. As normal cells undergo neoplastic transformation their metabolism and gene expression changes. Changes in glycosylation can modulate inflammatory responses, enable viral immune escape, promote cancer cell metastasis or regulate apoptosis.
Accuracy	Diagnostic accuracy is the ability of a test to detect a condition when it is present and the absence of a condition when it is absent.
Analyte	Target of interest. Substance whose chemical constituents are being identified and measured
Analyte Specific Reagent (ASR)	ASRs are regulated by the US Food and Drug Administration (FDA). The FDA created this regulatory status to ensure availability of individual reagents meeting specific quality requirements for clinical laboratories to use in developing Laboratory Developed Tests (LDTs). Many flow cytometry in vitro diagnostic tests fall into this category. This status is not recognised in countries outside of the United States
Antigen	Substance that causes the immune system to react, especially by producing antibodies
Bioinformatics	A scientific subdiscipline that involves using computer technology to collect, store, analyse and disseminate biological data
Biomarker	A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. May be used to see how well the body responds to a treatment. Also called molecular marker and signature molecule
College of American Pathologists (CAP) accredited	Ensures laboratories meet industry standards from CLIA, FDA and OSHA for test accuracy and patient diagnosis
Centers for Medicare & Medicaid Services (CMS)	The US federal authority responsible for regulating most laboratory testing performed on humans in the US through the Clinical Laboratory Improvement Amendments (CLIA) program
Clinical Laboratory Improvement Amendments (CLIA)	Certification required by clinical laboratories approved by the Center for Medicare and Medicaid Services (CMS) prior to human diagnostic testing
Clinical Utility	The ability of an assay to improve clinical decision-making and patient outcomes
Consumer Initiated Tests (CIT)	Laboratory testing that is initiated by the consumer without a physician order but reviewed and communicated back to the consumer via a physician
Cytology	The study of cells using a microscope
Direct to Consumer (DTC)	Laboratory testing that is initiated by the consumer without a physician order. The results are reported back directly to the consumer
ELISA	A laboratory technique that uses antibodies linked to enzymes to detect and measure the amount of a substance in a solution
Epitopes	A part of a molecule that an antibody will recognize and bind to
Exosome	Secreted nanovesicles that are present in all body fluids under both normal and pathophysiological conditions
Flow cytometry	A laboratory method that measures the number of cells, the percentage of live cells, and certain characteristics of cells, such as size and shape, in a sample of blood, bone marrow, or other tissue
Glycosylation	Glycosylation is enzyme-catalyzed process by which a carbohydrate is covalently attached to a target macromolecule, typically proteins and lipids. other carbohydrates, or other organic compounds. Put simply, Glycosylation is the attachment of carbohydrates to the backbone of a protein through an enzymatic reaction.
Glycosylation purpose	Glycosylation serves various functions. These include stabilizing proteins and supporting cell attachment to the extracellular matrix and protein–ligand interactions in the cell.
Immunoassay	A test that uses the bindng of antibodies to antigens to identify and measure certain substances
In vitro diagnostics (IVD)	Tests done on samples such as blood or tissue that have been taken from the human body to detect diseases or other conditions
Ligand	A molecule that binds to another (usually larger) molecule
Liquid Biopsy	Liquid biopsy is a minimally invasive biopsy method that uses molecules in body fluids as biomarkers,
Meteastatic cancer	In metastasis, cancer cells break away from the original (primary) tumor, travel through the blood or lymph system, and form a new tumor in other organs or tissues of the body.
Multi-omics	An approach where data sets of different omic groups are combined during analysis simultaneously
National Association of Testing Authorities (NATA)	The authority responsible for the accreditation of laboratories, inspection bodies, calibration services, producers of certified reference materials and proficiency testing scheme providers throughout Australia. It is also Australia's compliance monitoring authority for the OECD Principles of GLP. NATA provides independent assurance of technical competence through a proven network of best practice industry experts for customers who require confidence in the delivery of their products and services
Oncogene	A gene that is a mutated form of a gene involved in normal cell growth
Polygenic Risk Score (PRS)	Polygenic risk scores represent the total number of genetic variants an individual has that increase their risk of developing a particular disease.
Polymerase Chain Reaction (PCR)	A PCR test used to detect genetic material from a specific organism, such as a virus. RT-PCR test uses Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panels for detecting the presence of viral RNA
Recombinant	In genetics, describes DNA, proteins, cells, or organisms that are made by combining genetic material from two different sources
Sensitivity	Describes how well a test can detect a specific disease or condition in people who may actually have a disease or condition
Specificity	Refers to the % of people who test negative for a specific disease among a group of people who do not have a disease or condition
Surface plasmon resonance	A phenomenon where the electrons in the metal surface layer are excited by photons of incident light with a certain angle of incidence, and then propagate parallel to the metal surface. This optical phenomenon is used in SPR analysis to measure changes in mass of biomolecules immobilized on a metal film and is considered a highly sensitive technique for assessing binding kinetics and affinity as well as binding specificity.

Source: MST Access.

Appendix 2 – Tumour Markers

Exhibit 52: FDA-approved cancer biomarkers



Source: MST Access.

Exhibit 53: FDA-approved protein tumour markers currently used in clinical practice

Biomarker	Clinical use	Cancer type	Specimen	Methodology	Submission type	Year first approved or cleared	Device class	Product code
Pro2PSA	Discriminating cancer from benign disease	Prostate	Serum	Immunoassay	PMA	2012	3	OYA
OMA (HE4+CA-125)	Prediction of malignancy	Ovarian	Serum	Immunoassay	510(k)	2011	2	ONX
OVA1 (multiple proteins)	Prediction of malignancy	Ovarian	Serum	Immunoassay	510(k)	2009	2	ONX
HE4	Monitoring recurrence or progression of disease	Ovarian	Serum	Immunoassay	510(k)	2008	2	OIU
Fibrin/ fibrinogen degradation product (DR-70)	Monitoring progression of disease	Colorectal	Serum	Immunoassay	510(k)	2008	2	NTY
AFP-L3%	Risk assessment for development of disease	Hepatocellular	Serum	HPLC, microfluidic capillary electrophoresis	510(k)	2005	2	NSF
Circulating Tumor Cells (EpCAM, CD45, cytokeratins 8, 18+, 19+)	Prediction of cancer progression and survival	Breast	Whole blood	Immunomagnetic capture/ immune-fluorescence	510(k)	2005	2	NQI
p63 protein	Aid in differential diagnosis	Prostate	FFPE tissue	Immunohistochemistry	510(k)	2005	1	NTR
c-Kit	Detection of tumors, aid in selection of patients	GI stromal tumors	FFPE tissue	Immunohistochemistry	PMA	2004	3	NKF
CA19-9	Monitoring disease status	Pancreatic	Serum, plasma	Immunoassay	510(k)	2002	2	NIG
Estrogen receptor (ER)	Prognosis, response to therapy	Breast	FFPE tissue	Immunohistochemistry	510(k)	1999	2	MYA
Progesterone receptor (PR)	Prognosis, response to therapy	Breast	FFPE tissue	Immunohistochemistry	510(k)	1999	2	MXZ
HER-2/neu	Assessment for therapy	Breast	FFPE tissue	Immunohistochemistry	PMA	1998	3	MVC
CA-125	Monitoring disease progression, response to therapy	Ovarian	Serum, plasma	Immunoassay	510(k)	1997	2	LTK
CA15-3	Monitoring disease response to therapy	Breast	Serum, plasma	Immunoassay	510(k)	1997	2	MOI
CA27.29	Monitoring disease response to therapy	Breast	Serum	Immunoassay	510(k)	1997	2	MOI
Free PSA	Discriminating cancer from benign disease	Prostate	Serum	Immunoassay	PMA	1997	3	MTG
Thyroglobulin	Aid in monitoring	Thyroid	Serum, plasma	Immunoassay	510(k)	1997	2	MSW
Nuclear Mitotic Apparatus protein (NuMA, NMP22)	Diagnosis and monitoring of disease (professional and	Bladder	Urine	Lateral flow immunoassay	PMA	1996	3	NAH
Alpha-fetoprotein (AFP)b	Management of cancer	Testicular	Serum, plasma, amniotic fluid	Immunoassay	PMA	1992	3	LOK
Total PSA	Prostate cancer diagnosis and monitoring	Prostate	Serum	Immunoassay	PMA	1986	2	LTJ, MTF
Carcino-embryonic antigen	Aid in management and prognosis	Not specified	Serum, plasma	Immunoassay	510(k)	1985	2	DHX
Human hemoglobin (faecal occult blood)	Detection of fecal occult blood (home use)	Colorectal	Faeces	Lateral flow immunoassay	510(k) – CLIA waived	1976	2	KHE

Source: https://clinicalproteomicsjournal.biomedcentral.com/articles/10.1186/1559-0275-10-13/tables/1.

Appendix 3 – Exosome Isolation Methods

Exhibit 54: Methods for exosome isolation

Isolation method	Procedures	Advantages	Limitations
Ultracentrifugation	400 xg (to remove cells and large cell debris) 10,000-20,000xg (to remove large debris and intact organelles) 100,000-150,000 xg (to pellet exosomes)	Gold standard, obtain highly pure exosomal fraction	1. Only valid for exosomes purified from cell conditioned medium, but not the body fluids with complex mixture of many components 2. It sediments exosomes as well as other vesicles, proteins, and/or protein-RNA aggregates 3. Time-consuming, labour-intensive, and requires expensive equpiment
Size exclusion (filtration or chromatography)	Filtration through a series of filters down to 100 nm pore size followed by centrifugation (100,000 x *g*) to concentrate	Collect exosomes away from smaller protein contaminants	Risk of impurity or fragmentation of larger vesicles under filtration pressure
	Concentrated culture medium (CCM) or biofluid is dissolved in the mobile phase followed by passing through the stationary phase, wherein the various constituents of the mixture travel at different speeds so as to separate	Preserves the integrity and biological activity of exosomes	1. Deformation and breaking-up of larger vesicles, which may potentially skew results 2. Requiring a long run time, limiting its scalability for high-throughput applications
Immune affinity capture	Incubate CCM with specific microbeads to bind exosomes, separate exosome-bound micro-beads from CCM using solid support magnet or flow cytometry	Collect exosomes with specificity	Yields are often quite low
ExoQuick precipitation methods	This precipitation solution is combined with biofluid containing exosomes and is incubated overnight at 4°C. The mixture is then centrifuged at low speed to form a pellet containing exosomes	1. Enable high-throughput, quantitative isolation of exosomes from low samples volumes 2. No need for specialised equipment; shortens the operation time (just in less than 2 h) 3. Be efficient, reliable and reproducible	Co-precipitating non-vesicular contaminants, such as lipoproteins and polymer materials
Microfluidic technologies (ExoChip)	Immunoaffinity, sieving, and trapping exosomes on porous structures	Quantitative and high-throughput analysis of exosome contents with high sensitivity	Inadequate quality control and normalisation across study groups, not yet in clinical use

Source: Elucidating Methods for Isolation and Quantification of Exosomes: A Review; Kurian et al (20210)

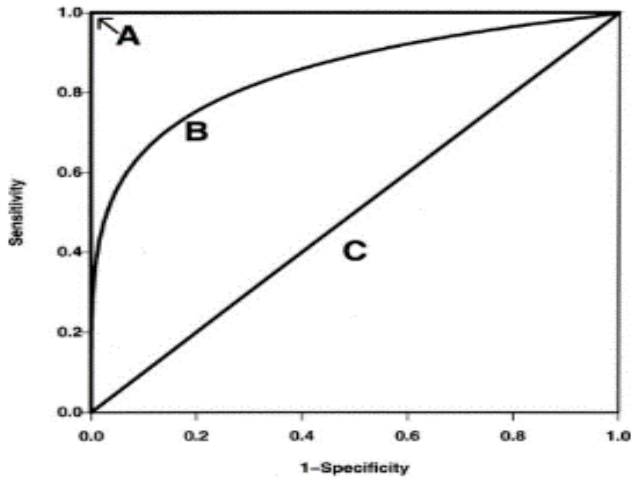
Appendix 4 – Area Under the ROC Curve (AUC)

Area Under the Curve (AUC) - Measuring the Accuracy of an In-vitro Diagnostic in development – Used to compare models and tests

The key metric commonly used to measure the accuracy of a diagnostic test is the percentage of true positives (sensitivity) to true negative (specificity) results it produces. This is usually captured and represented in the Receiver Operating Characteristic (ROC) curve, which plots the true positive rate (TPR) against the false positive rate. The true positive rate is the proportion of observations correctly predicted to be positive out of all positive observations (TP/(TP+FN)). The Area Under the Curve (AUC) in the plot is the summary measure from the ROC used to distinguish between classes.

A ROC curve is a graphical representation of the relationship between sensitive and cost (false positives) of a binary classifier. AUC is a summary of that relationship. The intent of the ROC curve is to show how well the model works for every possible threshold. ROC AUC is a measure of the separation between classes in a binary classifier.

Exhibit 55: Example of Receiver Operating Characteristic (ROC) curve



Source: https://www.ahajournals.org/doi/10.1161/circulationaha.105.594929 (As diagnostic test accuracy improves, the ROC curve m moves toward A, and the AUC approaches 1).

Appendix 5 – Top 20 Shareholders

Exhibit 56: Top 20 shareholders (as at 30 June 2022)

Ordinary Shareholders		Units	Percentag
THE TRUST COMPANY AUSTRALIA LIMITED <MOF A/C>		5,650,000	6.1
MOGGS CREEK PTY LTD <MOGGS CREEK SUPER A/C>		4,886,671	5.3
DR IRMGARD IRMINGER-FINGER		3,950,829	4.2
THE TRUST COMPANY (AUSTRALIA) LIMITED <MBF A/C>		2,048,333	2.2
BNP PARIBAS NOMINEES PTY LTD <IB AU NOMS RETAILCLIENT DRP>		2,021,843	2.2
LESAMOURAI PTY LTD		1,500,000	1.6
J P MORGAN NOMINEES AUSTRALIA PTY LIMITED		1,455,330	1.5
TRAOJ PTY LTD <TRAOJ A/C> 1,102,933		1,102,933	1.2
SUPERGUN PTY LTD <BRICKLANDING SUPER FUND A/C>		1,020,000	1.1
MR NATHAN RYAN WAGNER		1,010,433	1.1
DAVID NEATE		902,257	0.9
TROVEX PTY LTD		820,000	0.8
AJAVA HOLDINGS PTY LTD		819,461	0.8
KUNJOORUP PTY LTD		747,645	0.8
DR RUSSELL KAY HANCOCK		700,000	0.7
CITICORP NOMINEES PTY LIMITED		625,007	0.6
B & M LAWS SUPER FUND PTY LTD <B & M LAWS SUPER FUND A/C>		600,000	0.6
LL&P PTY LTD <THE ANDREW SOLOMONS S/F A/C>		574,095	0.6
MR PHILLIP RICHARD PERRY		561,000	0.6
MRS LYNNE MAREE WILKS		510,000	0.5
	Total	**31,505,837**	**34.24**

Source: INOVIQ.

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Level 13, 14 Martin Place, Sydney, NSW 2000
Main +61 2 8999 9988
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