1. Introduction

Olink® Oncology III is a reagent kit measuring 92 established and exploratory oncology related human protein biomarkers simultaneously. The analytical performance of the product has been carefully validated and the results are presented below.

1.1 TECHNOLOGY

The Olink reagents are based on the Proximity Extension Assay (PEA) technology[1-2], where 92 oligonucleotide labeled antibody probe pairs are allowed to bind to their respective target protein present in the sample. A PCR reporter sequence is formed by a proximity dependent DNA polymerization event, amplified, and subsequently detected and quantified using real-time PCR. The assay is performed in a homogeneous 96-well format without any need for washing steps, see Figure 1.

1.2 QUALITY CONTROLS

Internal and external controls have been developed by Olink for data normalization and quality control purposes. These controls have been designed to enable monitoring of the technical assay performance, as well as the quality of individual samples, providing information at each step of the Olink protocol (see Figure 1). The internal controls are added to each sample and include two Immunoassay controls, one Extension control and one Detection control. The Immunoassay controls (two non-human proteins) monitor all three steps starting with the immunoreaction. The Extension Control (an antibody linked to two matched oligonucleotides for immediate proximity independent of antigen binding) monitors the extension and read out steps and is used for data normalization across samples. Finally, the Detection control (a synthetic double-stranded template) monitors the readout step. Samples for which one or more of the internal control values deviate from a pre-determined range will be flagged and may be removed before statistical analysis.

An external control, inter-plate control (IPC), is included on each plate and used in a second normalization step. This control is made up of a pool of probes similar to the Extension control (Ext Ctrl), but generated with 92 matching oligonucleotide pairs. Furthermore, this improves inter-assay precision and allows for optimal comparison of data derived from multiple runs. The term "Normalized Protein eXpression" (NPX) refers to normalized data as described above.

1.3 DATA ANALYSIS

Data analysis was performed by employing a pre-processing normalization procedure. For each sample and data point, the corresponding Cq-value for the Extension control was subtracted, thus normalizing for technical variation within one run. Normalization between runs were then performed for each assay by subtracting the corresponding dCq-value for the Interplate Control (IPC) from the dCq-values generated. In the final step of the pre-processing procedure the values were set relative to a correction factor determined by Olink. The generated Normalized Protein eXpression (NPX) unit is on a log2 scale where a larger number represents a higher protein level in the sample, typically with the background level at around zero. Linearization of data is performed by the mathematical operation $2^{\wedge NPX}$. Coefficient of variation (CV) calculations were performed on linearized values.

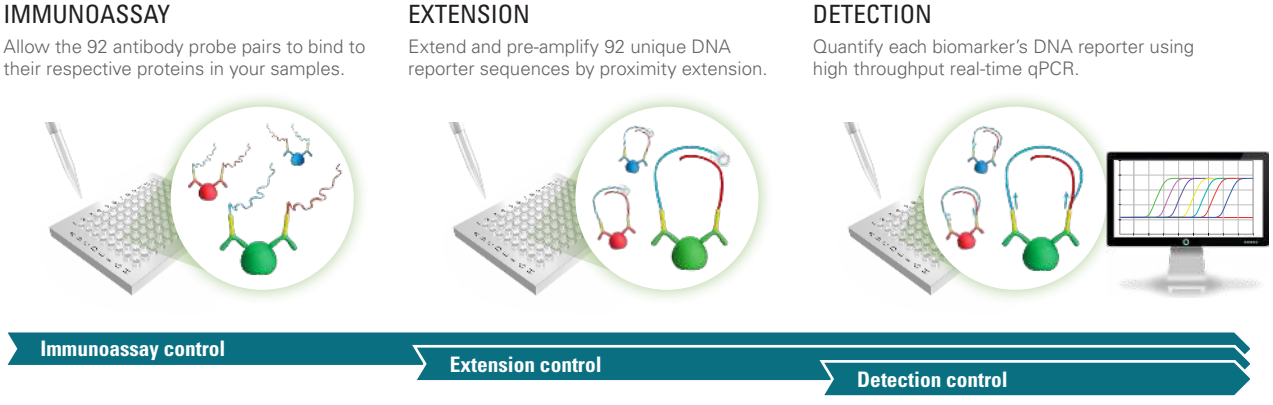

Fig 1. Olink assay procedure (above) and controls (below). The internal controls enable monitoring of the three core steps in the Olink assay and are used for quality control and data normalization. Read out is performed by using the Fluidigm® Biomark™ or the Fluidigm® Biomark™ HD system.

2. Performance characteristics

2.1 SAMPLE TYPES

The ability to use different sample types was evaluated with Olink Oncology III by collecting matched serum, EDTA, acid citrate dextrose (ACD), and sodium heparin plasma samples from 4 healthy individuals. Table 1 summarizes response values for 32 normal EDTA plasma samples expressed in NPX, as well as relative differences compared to EDTA plasma. Variations observed between responses in heparin, citrate plasma and serum, as compared to EDTA plasma, were generally small, and all assays will therefore function without limitation in these sample types. In addition, cell lysates, tissue lysates and CSF were also evaluated.

2.2 ANALYTICAL MEASUREMENT

DETECTION LIMIT

Calibrator curves were determined for 91 out of 92 biomarkers simultaneously in a multiplex format. One protein biomarker (Q93096) lacked accessible recombinant antigen. Limit of detection (LOD) was defined as 3 standard deviations above background and reported in pg/mL for all assays where recombinant protein antigen was available, see Table 1 and Figure 2.

HIGH DOSE HOOK EFFECT

The high dose hook effect is a state of antigen excess relative to the reagent antibodies, resulting in falsely lower values. In such cases, a significantly lower value can be reported which leads to misinterpretation of results. Therefore, the hook effect was determined for each analyte, here reported in pg/mL for 91 out of 92 assays, see Table 1.

MEASURING RANGE

The analytical measuring range was defined by the lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ) and reported in order of log10, see Table 1. The upper and lower limits of quantification, ULOQ and LLOQ, respectively were calculated with the following trueness and precision criteria; relative error ≤ 30% and CV ≤ 30%, of back-calculated values, and reported in pg/mL, see Table 1.

Three assays with their analytical data are shown in Figure 2 and the distribution of measuring ranges of 90 assays and endogenous plasma levels are shown in Figure 3. Separate calibrator curves established for each assay may be viewed at www.olink.com/onc3.

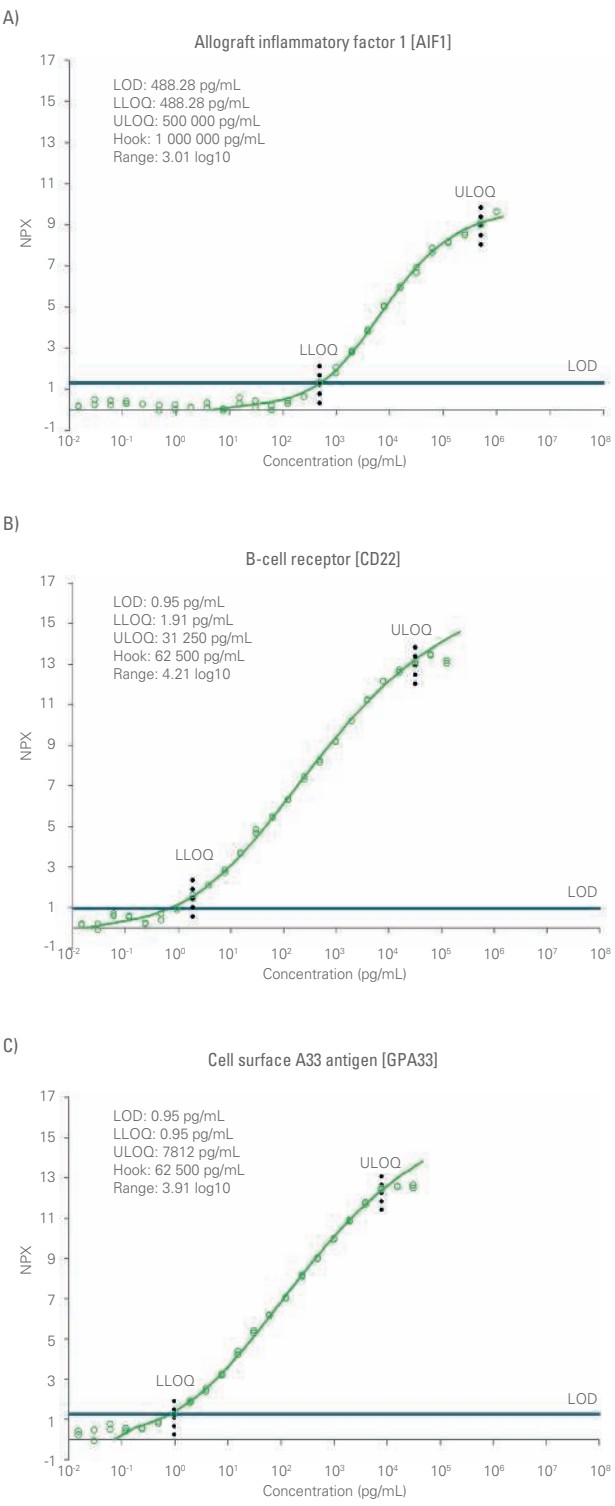

Fig 2. Calibrator curves from 3 assays and their corresponding analytical measurement data.

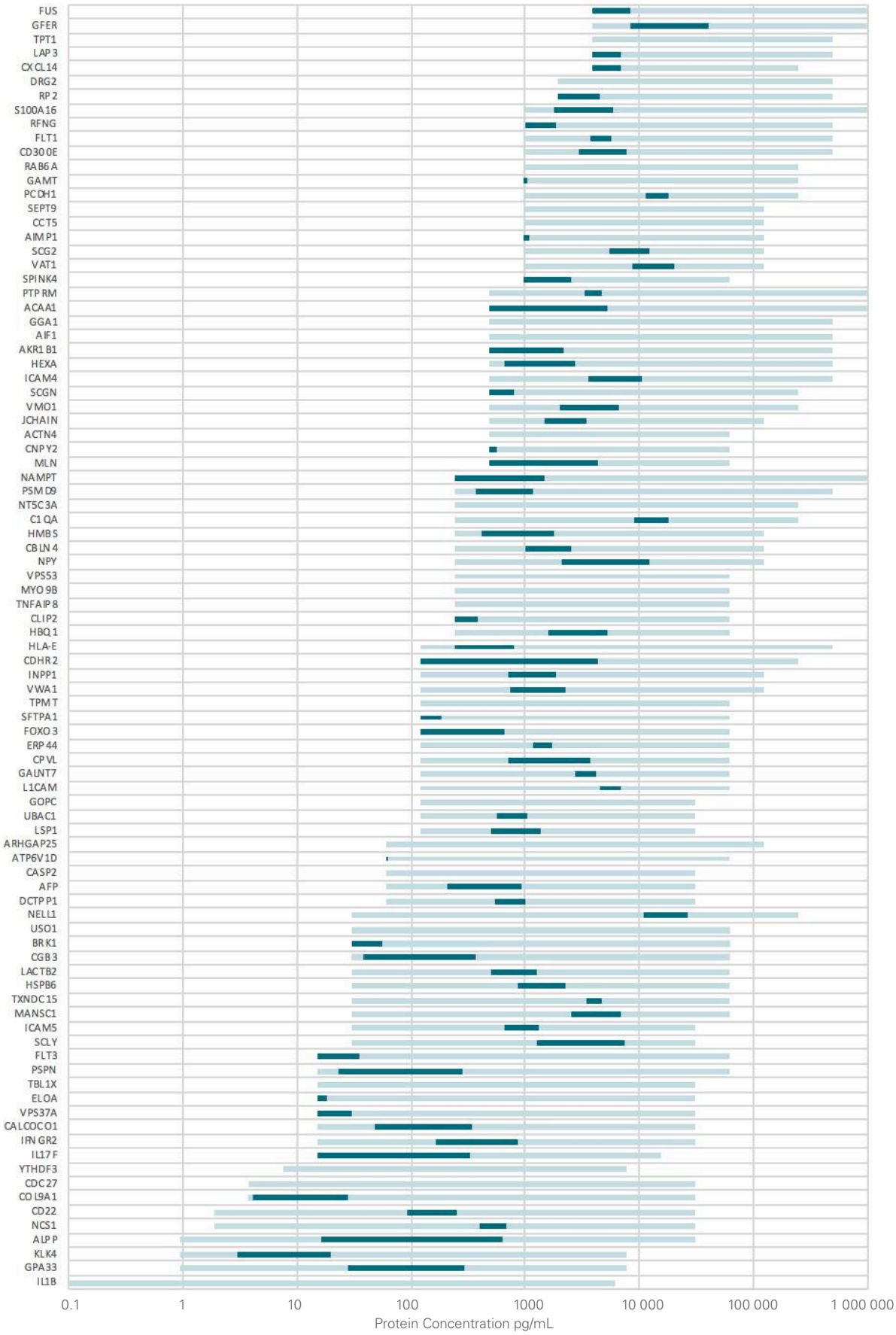

Fig 3. Distribution of analytical measuring range, defined by the lower and upper limits of quantification (LLOQ-ULOQ), and normal plasma levels (highlighted bars) for 91 out of 92 analytes.

Table 1. Sample Types; Normalized Protein eXpression (NPX), Endogenous Interference, Analytical Measurement; Limit of Detection (LOD), Lower Limit of Quantification (LLOQ), Upper Limit of Quantification (ULOQ), High Dose Effect (Hook), Range and Precision indicative of assay performance are shown for 92 analytes. Not available, NA

		Sample types						Endogenous Interference	Analytical measurement					Precision	
		Normal plasma levels (NPX)			Relative to EDTA plasma (%)			(mg/mL)	pg/mL				log10	% CV	
Target	UniProt No	10th %tile	Median	90th %tile	ACD	Heparin	Serum	Haemolysate	LOD	LLOQ	ULOQ	Hook	Range	Intra	Inter
26S proteasome non-ATPase regulatory subunit 9	O00233	1.6	2	2.8	50	46	127	0	244.14	244.14	500000	1000000	3.3	7	21
ADP-ribosylation factor-binding protein GGA1	Q9UJY5	NA	NA	0.4	NA	NA	NA	1.9	244.14	488.28	500000	1000000	3	6	22
Aldose reductase	P15121	1.8	2.5	4.2	74	65	76	0.9	244.14	488.28	500000	1000000	3	7	20
Alkaline phosphatase, placental type	P05187	4.3	6.2	9.3	156	152	171	15	0.48	0.95	31250	62500	4.5	6	17
Allograft inflammatory factor 1	P55008	NA	NA	1.1	111	110	127	15	488.28	488.28	500000	1000000	3	6	18
Alpha-actinin-4	O43707	NA	NA	NA	NA	NA	NA	15	488.28	488.28	62500	500000	2.1	5	17
Alpha-fetoprotein	P02771	3.6	4.5	5.6	102	102	108	15	61.04	61.04	31250	62500	2.7	7	24
Aminoacyl tRNA synthase complex-interacting multifunctional protein 1	Q12904	0.3	0.9	1.2	112	96	93	0.9	488.28	976.56	125000	500000	2.1	7	18
B-cell receptor CD22	P20273	6	6.8	7.5	89	96	106	15	0.95	1.91	31250	62500	4.2	5	19
Beta-1,3-N-acetylglucosaminyltransferase radical fringe	Q9Y644	1.6	1.9	2.3	97	90	130	15	488.28	976.56	500000	1000000	2.7	6	19
Beta-hexosaminidase subunit alpha	P06865	1.4	1.7	2.4	94	134	120	15	488.28	488.28	500000	1000000	3	7	20
Cadherin-related family member 2	Q9BYE9	0.8	2	5.5	62	63	89	15	122.07	122.07	250000	500000	3.3	8	21
Calcium-binding and coiled-coil domain-containing protein 1	Q9P1Z2	2.5	3.9	5	116	110	62	0	7.63	15.26	31250	62500	3.3	8	19
CAP-Gly domain-containing linker protein 2	Q9UDT6	1.2	2	2.3	110	55	32	15	122.07	244.14	62500	1000000	2.4	9	22
Caspase-2	P42575	NA	NA	0.7	118	131	136	15	15.26	61.04	31250	62500	2.7	5	17
Cell division cycle protein 27 homolog	P30260	NA	NA	NA	NA	NA	NA	7.5	3.81	3.81	31250	62500	3.9	6	21
Cell surface A33 antigen	Q99795	5	6.7	8.4	91	103	112	15	0.95	0.95	7812	62500	3.9	5	21
Cerebellin-4	Q9NTU7	2.5	3.1	3.6	96	142	116	15	244.14	244.14	125000	500000	2.7	8	26
Choriogonadotropin subunit beta 3	P0DN86	2.3	3.9	5.2	96	106	103	15	15.26	30.52	62500	125000	3.3	5	18
CMRF35-like molecule 2	Q496F6	2.2	2.8	3.4	97	102	116	15	976.56	976.56	500000	1000000	2.7	6	22
Collagen alpha-1(IX) chain	P20849	1	1.7	2.5	108	96	107	15	3.81	3.81	31250	62500	3.9	7	20
Complement C1q subcomponent subunit A	P02745	5.6	6.1	6.7	128	100	115	15	244.14	244.14	250000	500000	3	5	18
C-X-C motif chemokine 14	O95715	0.3	1.5	2.3	NA	NA	NA	15	1953.12	3906.25	250000	500000	1.8	10	19
Cytosol aminopeptidase	P28838	NA	0.4	2.1	53	52	49	0.9	976.56	3906.25	500000	1000000	2.1	5	18
Cytosolic 5'-nucleotidase 3A	Q9H0P0	NA	0.8	1.3	87	92	85	0	244.14	244.14	250000	1000000	3	10	22
dCTP pyrophosphatase 1	Q9H773	3.8	4.3	4.7	115	137	114	3.8	30.52	61.04	31250	62500	2.7	5	20
Developmentally-regulated GTP-binding protein 2	P55039	NA	NA	0.5	NA	NA	NA	0.9	1953.12	1953.12	500000	1000000	2.4	8	16
Elongin-A	Q14241	NA	NA	1	NA	NA	NA	1.9	15.26	15.26	31250	62500	3.3	6	17
Endoplasmic reticulum resident protein 44	Q9BS26	3.7	4	4.2	97	99	108	15	122.07	122.07	62500	250000	2.7	6	19
Endoribonuclease LACTB2	Q53H82	2.8	3.3	4	65	62	77	0	30.52	30.52	62500	500000	3.3	5	17
FAD-linked sulfhydryl oxidase ALR	P55789	1.8	2.5	3.8	90	76	92	7.5	3906.25	3906.25	4000000	8000000	3	6	18
F-box-like/WD repeat-containing protein TBL1X	O60907	NA	NA	0.4	NA	NA	NA	15	15.26	15.26	31250	62500	3.3	6	21
Forkhead box protein O3	O43524	NA	0.9	2.7	85	92	114	15	61.04	122.07	62500	500000	2.7	6	21
General vesicular transport factor p115	O60763	NA	NA	0.9	71	47	54	0.5	30.52	30.52	62500	125000	3.3	6	21
Golgi-associated PDZ and coiled-coil motif-containing protein	Q9HD26	0.2	0.7	1.1	56	52	56	15	30.52	122.07	31250	62500	2.4	6	20
Guanidinoacetate N-methyltransferase	Q14353	NA	NA	1.1	NA	NA	NA	15	976.56	976.56	250000	500000	2.4	7	15
Heat shock protein beta-6	O14558	4.5	5.3	6	129	161	166	15	30.52	30.52	62500	500000	3.3	5	24
Hemoglobin subunit theta-1	P09105	2.2	2.8	4	24	31	61	0	244.14	244.14	62500	125000	2.4	5	21
HLA class I histocompatibility antigen, alpha chain E	P13747	1.1	1.5	2.1	105	104	48	15	61.04	122.07	500000	1000000	3.6	9	22
Immunoglobulin J chain	P01591	2.8	3.3	4	100	112	120	15	488.28	488.28	125000	250000	2.4	4	25
Inositol polyphosphate 1-phosphatase	P49441	2.8	3.5	4.1	105	85	70	15	122.07	122.07	125000	500000	3	6	22
Intercellular adhesion molecule 4	Q14773	3.6	4.7	5.4	95	102	107	0.9	488.28	488.28	500000	1000000	3	9	22
Intercellular adhesion molecule 5	Q9UMF0	5	5.5	5.9	95	98	96	15	15.26	30.52	31250	62500	3	5	21
Interferon gamma receptor 2	P38484	3.9	4.5	6.1	93	98	118	15	15.26	15.26	31250	62500	3.3	7	20
Interleukin-1 beta	P01584	NA	NA	1.7	105	106	149	15	0.01	0.05	6250	12500	5.1	8	15
Interleukin-17F	Q96PD4	NA	NA	2.8	95	83	94	15	7.63	15.26	15625	62500	3	5	18
Kallikrein-4	Q9Y5K2	2.3	3.1	4.6	102	112	111	15	0.95	0.95	7812	62500	3.9	7	19

		Sample types						Endogenous Interference	Analytical measurement					Precision	
		Normal plasma levels (NPX)			Relative to EDTA plasma (%)			(mg/mL)	pg/mL				log10	% CV	
Target	UniProt No	10th %tile	Median	90th %tile	ACD	Heparin	Serum	Haemolysate	LOD	LLOQ	ULOQ	Hook	Range	Intra	Inter
Lymphocyte-specific protein 1	P33241	3.1	3.6	4.5	95	139	199	15	30.52	122.07	31250	62500	2.4	5	22
MANSC domain-containing protein 1	Q9H8J5	5.8	6.7	7.2	94	91	91	15	30.52	30.52	62500	125000	3.3	5	23
N-acetylgalactosaminyltransferase 7	Q86SF2	4.6	4.8	5.2	101	125	80	15	122.07	122.07	62500	1000000	2.7	6	22
Neural cell adhesion molecule L1	P32004	6.5	6.7	7	97	103	111	15	30.52	122.07	62500	125000	2.7	4	20
Neuronal calcium sensor 1	P62166	6.9	7.5	7.7	119	132	157	0.9	1.91	1.91	31250	62500	4.2	6	19
Nicotinamide phosphoribosyltransferase	P43490	0.9	1.3	2.7	68	93	265	0.9	244.14	244.14	1000000	1000000	3.6	8	18
peroxisomal 3-ketoacyl-CoA thiolase	P09110	1.5	2.1	5.2	90	92	92	15	244.14	488.28	1000000	1000000	3.3	7	23
Persephin	O60542	2.1	3.9	5	111	81	94	15	7.63	15.26	62500	125000	3.6	12	19
Porphobilinogen deaminase	P08397	1.8	2.7	3.5	49	44	129	0	122.07	244.14	125000	500000	2.7	5	18
Probable serine carboxypeptidase CPVL	Q9H3G5	3.7	4.9	6	78	120	123	15	30.52	122.07	62500	125000	2.7	7	27
Promotilin	P12872	1	3.5	4.5	117	126	114	15	244.14	488.28	62500	500000	2.1	5	23
Pro-neuropeptide Y	P01303	3.3	5.2	6.2	97	42	27	1.9	244.14	244.14	125000	500000	2.7	7	27
Protein BRICK1	Q8WUW1	0.7	1	1.3	116	97	108	15	30.52	30.52	62500	125000	3.3	6	20
Protein canopy homolog 2	Q9Y2B0	NA	NA	1.4	NA	NA	NA	15	488.28	488.28	62500	1000000	2.1	7	19
Protein kinase C-binding protein NELL1	Q92832	8	8.5	9.2	94	107	113	15	15.26	30.52	250000	500000	3.9	6	19
Protein S100-A16	Q96FQ6	1.8	2.2	3.2	87	104	122	3.8	976.56	976.56	1000000	4000000	3	9	19
Protein tyrosine phosphatase type IVA 1	Q93096	1.3	1.8	2.6	91	93	98	15	NA	NA	NA	NA	NA	9	19
Protein XRP2	O75695	0.8	1.3	1.6	102	81	96	0.9	1953.12	1953.12	500000	1000000	2.4	5	17
Protocadherin-1	Q08174	4.6	4.9	5.1	115	132	142	15	976.56	976.56	250000	1000000	2.4	5	19
Pulmonary surfactant-associated protein A1	Q8IWL2	NA	1.1	2.1	91	79	92	15	30.52	122.07	62500	125000	2.7	6	20
Ras-related protein Rab-6A	P20340	NA	NA	1.2	NA	NA	NA	15	976.56	976.56	250000	500000	2.4	6	23
Receptor-type tyrosine-protein kinase FLT3	P36888	0.9	1.7	2.1	92	122	147	15	15.26	15.26	62500	125000	3.6	8	22
Receptor-type tyrosine-protein phosphatase mu	P28827	3.8	4.1	4.4	91	109	121	15	244.14	488.28	1000000	1000000	3.3	7	22
Rho GTPase-activating protein 25	P42331	NA	NA	1	NA	NA	NA	15	15.26	61.04	125000	500000	3.3	6	20
RNA-binding protein FUS	P35637	NA	0.8	1.7	102	113	122	15	3906.25	3906.25	4000000	8000000	3	7	22
Secretagogin	O76038	1.4	2.3	2.9	116	115	114	15	488.28	488.28	250000	1000000	2.7	8	21
Secretogranin-2	P13521	3.5	4.3	5	102	119	86	15	976.56	976.56	125000	500000	2.1	5	21
Selenocysteine lyase	Q96I15	6.3	6.9	8.9	104	91	111	15	15.26	30.52	31250	62500	3	5	21
Septin-9	Q9UHD8	NA	NA	NA	NA	NA	NA	15	488.28	976.56	125000	500000	2.1	7	19
Serine protease inhibitor Kazal-type 4	O60575	NA	0.7	2.6	88	100	112	15	488.28	976.56	62500	125000	1.8	6	20
Synaptic vesicle membrane protein VAT-1 homolog	Q99536	3.6	4.2	4.9	102	117	128	15	488.28	976.56	125000	500000	2.1	4	22
T-complex protein 1 subunit epsilon	P48643	NA	NA	0.2	NA	NA	NA	0.9	488.28	976.56	125000	500000	2.1	6	18
Thiopurine S-methyltransferase	P51580	NA	NA	NA	NA	NA	NA	0.2	122.07	122.07	62500	125000	2.7	6	18
Thioredoxin domain-containing protein 15	Q96J42	8.2	8.5	8.6	110	108	106	15	30.52	30.52	62500	125000	3.3	4	18
Translationally-controlled tumor protein	P13693	NA	NA	NA	NA	NA	NA	3.8	1953.12	3906.25	500000	1000000	2.1	9	19
Tumor necrosis factor alpha-induced protein 8	O95379	NA	NA	0.8	NA	NA	NA	15	244.14	244.14	62500	500000	2.4	6	21
Ubiquitin-associated domain-containing protein 1	Q9BSL1	2.9	3.1	3.8	38	42	91	0	122.07	122.07	31250	62500	2.4	5	19
Unconventional myosin-IXb	Q13459	NA	0.4	0.7	133	87	102	7.5	122.07	244.14	62500	125000	2.4	6	19
Vacuolar protein sorting-associated protein 37A	Q8NEZ2	NA	0.2	1	102	93	67	0.9	15.26	15.26	31250	62500	3.3	6	20
Vacuolar protein sorting-associated protein 53 homolog	Q5VIR6	NA	NA	0.3	88	NA	70	15	244.14	244.14	62500	500000	2.4	6	18
Vascular endothelial growth factor receptor 1	P17948	2.2	2.5	2.7	104	90	98	15	976.56	976.56	500000	1000000	2.7	6	20
Vitelline membrane outer layer protein 1 homolog	Q7Z5L0	2.4	3.1	4	107	110	117	15	488.28	488.28	250000	500000	2.7	6	20
von Willebrand factor A domain-containing protein 1	Q6PCB0	3.8	4.4	5.3	96	102	121	15	61.04	122.07	125000	500000	3	7	19
V-type proton ATPase subunit D	Q9Y5K8	NA	0.2	0.7	NA	NA	NA	0.9	30.52	61.04	62500	125000	3	8	21
YTH domain-containing family protein 3	Q7Z739	NA	NA	NA	NA	NA	NA	15	3.81	7.63	7812	62500	3	7	21

2.3 PRECISION

REPEATABILITY

Intra-assay variation (within-run) was calculated as the mean %CV for 6 individual samples run in triplicates within each of 9 separate runs during the validation studies. Inter-assay variation (between runs) was calculated between experiments with the same operator. The reported inter-assay %CV is the average of three operators' %CV. Variation calculations were performed on linearized values for 92 analytes for which response levels could be measured in serum and normal plasma, see Table 1.

Across all 92 assays, the mean intra-assay and inter-assay variations were observed to be 6.4% and 20.1%, respectively. The distribution of both intra-assay and inter-assay variations are shown in Figure 4.

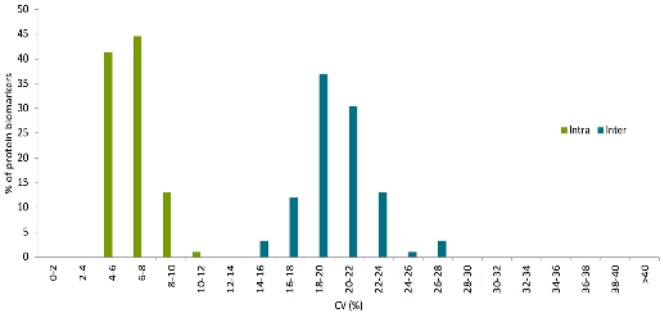

Fig 4. Distribution of intra-assay and inter-assay variations of Olink Oncology III

REPRODUCIBILITY

Inter-site variations (between-site) were investigated during the validation of previous panels in beta-site studies to estimate the expected variations in values between different laboratories, with different operators and using different equipment. The beta-site studies have previously shown reproducibility and repeatability in line with Olink Bioscience results, and were therefore not performed for Olink Oncology III. For information on performed beta-site studies, download our Data Validation documents at www.olink.com/data-validation.

2.4 ANALYTICAL SPECIFICITY

ASSAY SPECIFICITY

To test that the antibodies selected for use in our Olink Oncology III assays are specific for their desired targets, we measured each assay response to all of the 92 panel-specific proteins, as well as against an additional 107 proteins (not shown). In principle, the specificity is tested by creating a test sample, consisting of a pool of antigens, which is then incubated with all 92 antibody probe pairs from the panel. Only if there is a correct match will a reporter sequence be created and serve as a template for subsequent real-time qPCR. Ten sub-pools of antigen are evaluated to cover the 92 assays in Olink, see Figure 5. None of the Olink Oncology III showed significant signal from the proteins tested.

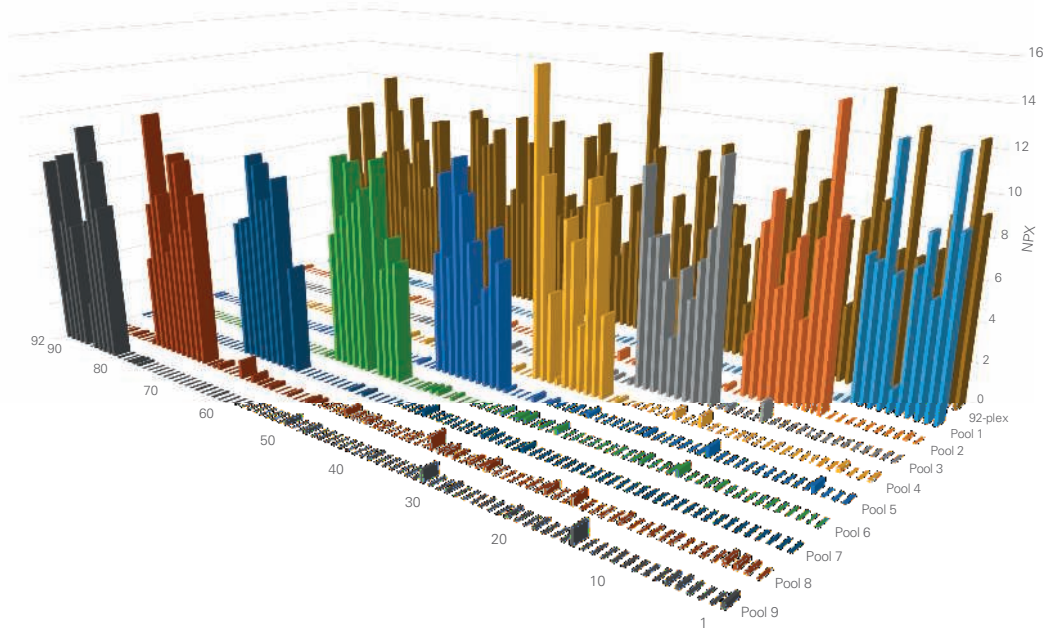

Fig 5. Assay readout specificity of the Olink platform. For each assay, specificity is confirmed by testing antigen sub-pools against the complete 92-plex pool as to each sub-mix.

ENDOGENOUS INTERFERENCE

Endogenous interference from heterophilic antibodies, e.g. human anti-mouse antibody (HAMA), and rheumatoid factor are known to cause problems in some immunoassays. Evaluation of the potential impact of this specific interference has been performed previously using a special "mismatch" system. The only way to generate a signal in this system is by antibody probe pairs being brought into proximity, by cross-binding substances other than antigens, e.g. heterophilic antibodies and similarly acting rheumatoid factor. No interference due to HAMA or RF could be detected for any of the samples in any of the previously tested panels, indicating sufficient blocking of these agents (data not shown).

Fig 6. Endogenous interference. Levels tested for hemolysate were 0.23-15 g/L hemoglobin. The highest hemolysate concentration translates to about 10% hemolysis.

The potential impact of bilirubin, lipids and hemolysate, known interfering plasma and serum components, were evaluted at different added concentrations. An example of hemolysate levels tested is shown in Figure 6. These additions represent different patient health conditions and/or sample collection irregularities. Interference by bilirubin and lipids has previously been evaluated, and disturbance has only been observed at extrem levels corresponding to 8 or 10 times normal [3, 4] values and therefore not performed for Olink Oncology III. In 31 out of 92 assays, altered signal was observed by the addition of hemolysate. The reason is most likely due to actual analyte leaking out of the disrupted blood cells. A concentration of 15 g/L of hemolysate represents 10% hemolysis of a sample. Table 1 reports the highest concentration of hemolysate that does not have an impact on assay performance.

2.5 SCALABILITY

Assay performance was further evaluated with regard to scalability, meaning the capability of the Olink technology to maintain the same quality of performance irrespective of multiplex level. Previously, we have shown that a step-wise increase of multiplex grade (8, 24, 48, 72 and 96) does not compromise assay performance (data not shown). To further strengthen that Olink provides consistent results, single assays for Growth Hormone (GH) and Matrix Metalloproteinase (MMP-7) were compared when run in a full 96-plex reaction. The results for each assay and their observed dCq-values were plotted against the entire 96-plex reaction. The square of the correlation coefficient (R^2) value was generated by linear regression.

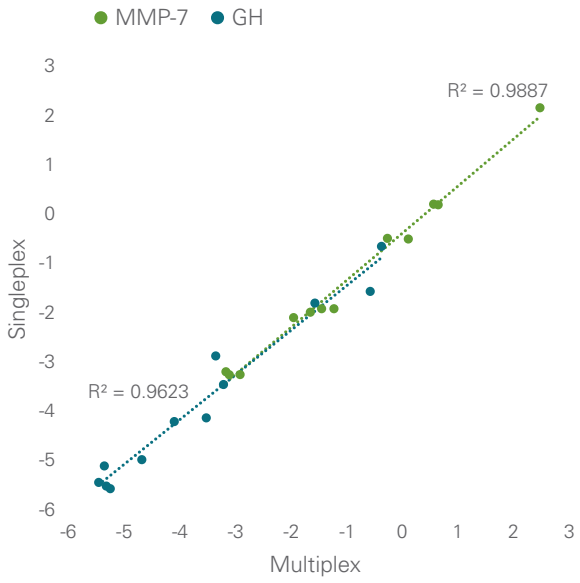

Fig 7. Scalability of the Olink technology platform. The experiment was performed using the Olink CVD II panel. Human plasma samples were analyzed in singleplex for Growth Hormone (GH) and Matrix Metalloproteinase (MMP-7) with the equivalent assays performed in a full 96-plex reaction. The observed dCq (log2) values were plotted, and the correlation coefficient R^2 value was generated by linear regression.

3. References

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