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Methods: Xmal-RRBS dataset for 34 TNBC biopsies taken prior to NAC was used. Virtual amplicons were designed under the following criteria: at least two MSRE (BstHII and/or HpaII) recognition sites within the amplicon, the amplicon length no more than 100 bp to provide high MSRE-qPCR efficiency, the average difference in the methylation level between adjacent CpG pairs no more than 10%. To select amplicons, MSRE sites were hierarchically clustered with the distance metric of physical distance over the genome and the difference in their methylation level, followed by complete-linkage agglomeration to prevent lengthening of amplicons via chaining phenomenon. Diagnostic potential was assessed with cross-validated AUC. Markers with AUC \geq 75% were selected to form panels.

Results: Genes APCDD1L, RUSC1-AS1, MYO15B, EXOC2, THBS2, MXRA5, ANKRD64 were selected to form possible combinations of markers. Eventually, 120 combinations of amplicons panels that discriminate NAC response were obtained and top-10 are shown in the table.

Table: 1143P Top 10 combinations of amplicons that discriminate NAC responding and non-responding TNBC sorted in descending order by AUC. Three gene (RUSC1-AS1, MYO15B, ANKRD46) panel exhibits highest value for AUC, sensitivity and specificity

Panels	AUC, %	Sensitivity, %	Specificity, %	Accuracy, %
RUSC-AS1, MYO15B, ANKRD46	91	89	83	85
APCDD1L, RUSC1-AS1	88	96	61	77
RUSC1-AS1, MYO15B, MXRA5, ANKRD46	88	82	85	84
APCDD1L, RUSC-AS1, MYO15B	88	81	81	81
APCDD1L, RUSC-AS1, ANKRD46	88	93	69	80
RUSC1-AS1, MYO15B, THBS2, ANKRD46	87	81	84	82
APCDD1L, RUSC1-AS1, THBS2	87	89	65	76
APCDD1L, MYO15B, THBS2	87	77	88	83
RUSC1-AS1, THBS2, MXRA5, ANKRD46	86	82	82	82
RUSC1-AS1, EXOC2	86	76	88	83

Conclusions: Our approach shows promising results for designing multiplex MSRE-qPCR panels to accurately predict TNBC response to NAC. Further verification of its efficacy is required on validation cohorts.

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1144P When AI-based image analysis gets in clinical trials

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Background: Especially during the COVID-19 pandemic, implementation and development of whole slide scanning lead to an active growth of digital pathology and image analysis (IA). In the present study, we retrospectively conducted a global evaluation of three Breast cancer markers: ER, PR and Ki67 with the aim to study the correlation between pathologist conventional semi quantitative scoring method on glass and scanned slides versus artificial intelligence-based IA.

Methods: Study samples were scored independently either by five independent pathologists on scanned images and glass slides, or using supervised IA algorithms (IA results validated by pathologists). The readout for the three markers was the percentage of tumor positives stained cells. The correlation between the pathologist evaluation on glass slides versus scanned images was calculated using Pearson's correlation coefficient. Pathologist's evaluations and IA results were compared using Intraclass Correlation Coefficient (ICC). Additionally, the average time spent by the pathologist per sample was measured for each evaluation method.

Results: The correlation of pathologist evaluation between glass slide and scanned image showed a Pearson's correlation coefficient \geq 0.90 for each marker. The ICC between IA algorithm and pathologist was on average over 0.8 for the three markers, showing a good agreement between the different scoring method. However, some challenges were identified related to the detection of tumor area that needed some additional pathologist review for specific complex cases. Overall, time required by the pathologist for a complete evaluation decreased by roughly 3 times when supported by image analysis tools.

Conclusions: Based on the Pearson's correlation coefficient and the ICC results, we observe an equivalence in the pathologist conventional scoring (Image or glass slides)

and the use of IA. In an era where regulations are still being discussed for the use of algorithm by the FDA (AI-Based or not), we can *mitigate* regulatory requirements by having pathologists reviewing the results of a digital analysis. We conclude here to a benefit from the combination of pathologist evaluation and IA in terms of time with at least equivalent results in terms of accuracy.

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1145P Reliable detection of BRCA1 and BRCA2 large genomic rearrangements in FFPE tissue: A new diagnostic benchmark for somatic BRCA testing

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Background: PARP inhibitors are used for treatment of tumors lacking function of the double-strand DNA break repair proteins BRCA1 or BRCA2 and are already approved for several cancer types. Thus, it is clinically crucial to determine germline as well as somatic *BRCA1/2* mutations in those patients. The amplicon-based OncoPrint *BRCA1* and *BRCA2* Assay is a test routinely used in diagnostics with FFPE specimens. The assay is validated for the detection of mutations, however, data on its performance in detecting large genomic rearrangements in FFPE tissue, is scarce.

Methods: We cross-validated OncoPrint *BRCA1* and *BRCA2* Assay in blood samples and/or FFPE tissue with multiplex ligation-dependent probe amplification (MLPA) for exon deletions and OncoScan, and an in-house hybridization-based target capture NGS assay (MelArray) with a customized pipeline for the detection of loss of heterozygosity (LOH) and heterozygous versus complete gene loss.

Results: The OncoPrint *BRCA1* and *BRCA2* Assay could detect both exon deletion and mono- and bi-allelic losses of the *BRCA1/2* genes in samples with tumor content greater than 40%. We show that the therapeutically relevant large genomic rearrangements are reliably detected with the amplicon-based OncoPrint *BRCA1* and *BRCA2* Assay in FFPE tumor tissue.

Conclusions: Based on our data, we suggest somatic *BRCA* testing as standard diagnostic prescreening prior to germline *BRCA* testing. Thus, a rapid, reliable and affordable sBRCA testing could be used in the future as standard analysis after diagnosis with ovarian, breast, pancreatic and prostate cancer in routine diagnostics. This will immensely shorten the time for treatment decision, especially for patients without *BRCA1/2* alterations since generally only patients with sBRCA mutations will be referred to the more time consuming genetic counselling and germline (gBRCA) testing.

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1146P Closing the target gap: A computational approach to optimizing therapeutic selection for cancer patients

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Background: While significant progress has been made in developing new therapies for cancer patients, many patients lack treatments that result in favorable outcomes. Existing patient-therapy matching algorithms frequently rely on mutations or other well-studied targets for which limited FDA-approved therapies exist. In contrast, SHEPHERD's approach, called DELVE, uses computational and mathematical tools informed by transcriptomic data to match therapies with the models, cancers, and specific patients that will be most impacted by drug treatment, regardless of mutational status.

Methods: DELVE leverages bioinformatics, cheminformatics, proprietary algorithms, deep learning neural networks, random forest classifiers, and other tools to generate transcriptomic-level drug response-resistance signatures. DELVE was deployed to characterize drug response and resistance across thousands of *in vivo*, *ex vivo*, and *in vitro* cancer models and over 75,000 patient samples representing 125 cancers and healthy tissues.

Results: DELVE was able to correctly classify the highest and lowest responding drug-cell line pairs with 96% sensitivity [CI +/- 0.34%] and 88% specificity [CI +/- 1.71%].