Now featuring six Hallmarks of Cancer

clara™ Total mRNA Report

Complex biologies, intelligently simplified.

ALMAC

Partnering to Advance Human Health

clara^{T} is a unique software-driven solution, classifying biologically relevant gene expression signatures into a comprehensive, easy-to-interpret report.

clara^{T} benefits at a glance:

- Maximises the understanding of your dataset
- Provides readouts for the most relevant published gene expression signatures
- Standardises comparisons between different datasets
- Highlights consensus between multiple gene expression signatures
- Multiple signatures from a single tumour sample
- Cost effective solution, saving analysis time

The opportunity created by RNA-Sequencing:

- RNA-Sequencing (RNA-Seq) is an untapped resource for biomarker discovery and development in oncology enabling the discovery and validation of an endless combination of gene expression signatures
- Gene expression signatures are more dynamic than DNA based biomarkers and better reflect changes in biology as a tumour adapts to multiple treatments
- RNA-Seq can also be used for detection of novel gene fusions and alternative transcripts

Hannah Millar, Senior Laboratory Scientist

The challenges of RNA-Sequencing:

However, there are some inherent challenges with high throughput RNA-Seq. These include:

- Complex data outputs that require advanced computational bioinformatics pipelines to develop and validate robust gene expression assays
- Analysis of multiple signatures and biologies can be time consuming, requiring significant bioinformatics / statistical resource
- There are still no PMA approved gene expression assays creating a potential regulatory risk for companies considering this approach

clara^{T*} Report:

clara^{T} is a unique reporting solution to help cancer researchers overcome the challenges associated with RNA-Seq and analysis. Samples can be sent to Almac's Labs for processing and automated generation of the clara^{T} report.

clara^{T} classifies publicly available gene expression signatures and single gene targets linked to multiple key biologies, alongside Almac's own proprietary assays, according to the 10 Hallmarks of Cancer. Originally published by Douglas Hanahan and Robert Weinberg in 2000. Clients are provided with a unique, interactive report that allows the easy visualisation of the key discriminating biologies within both the study cohort and an individual tumour sample.

A pan-cancer solution, based on a powerful bioinformatics pipeline, automatically generating the clara^{T} report from raw gene expression data utilising our Next Generation Sequencing (NGS) service.

* **clara^{T}** is for research use only (RUO) and is not to be used for diagnostic or prognostic purposes, including predicting responsiveness to a particular therapy

clara^{T} benefits:

Maximises the understanding of your data set – Enables you to instantly find the most important patterns from your RNA-Seq data that will inform your research going forward.

Provides readouts for the most relevant published gene expression signatures – Easy-to-interpret gene expression scores are displayed in the report for the most important signatures published in leading cancer journals. Providing instant information on how they perform in your dataset.

Standardises comparisons between different datasets – By providing reproducible Hallmark classifications in an automated fashion, data analysis is standardised across multiple cohorts, removing variation between different discovery approaches.

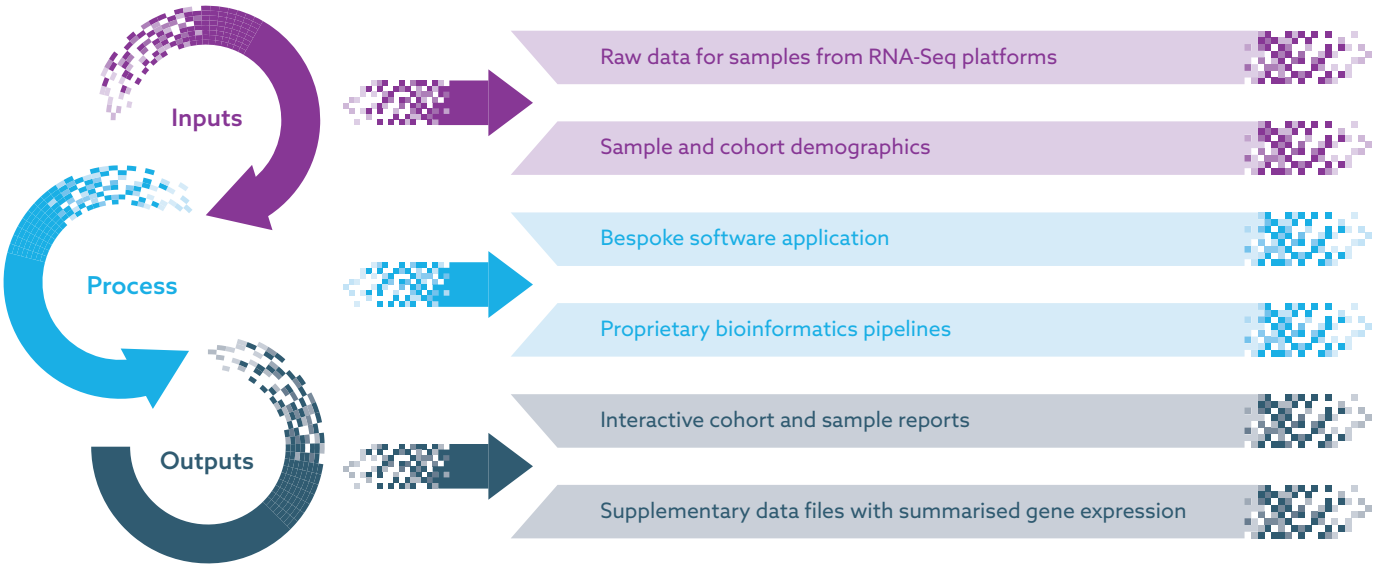
Highlights consensus between multiple gene expression signatures – The ability to simultaneously visualise multiple different gene expression signature readouts enables a consensus analysis approach resulting in greater confidence in data interpretation.

Multiple signatures from a single tumour sample – A single sample sent to Almac for profiling, sequenced on an optimised NGS technology platform, with a powerful bioinformatics pipeline producing multiple signature readouts. Saving precious tissue samples, time and cost.

Cost effective solution, saving analysis time – Cancer researchers can benefit from detailed, actionable analysis of RNA-Seq data from the report without investing in additional significant time and resource to perform in-house bioinformatics analysis.

Cain Diver, Laboratory Scientist

clara^{T} workflow:



clara^{T} Cohort Report:

The **clara^{T} Cohort Report** and **interactive heat map** simplifies visualisation of expression levels across a range of the most relevant published multigene signatures allowing for quick and easy interpretation of results.

The signatures are classified across the Hallmarks of Cancer.

Advantages of the clara^{T} Cohort Report:

- Discover patterns of gene expression within your cohort
- Identify unique molecular subgroups within your dataset
- Determine groups of consensus gene expression signatures
- Highlight any differences or unexplained anomalies between samples


1 Research Use Only

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Client Information & Cohort Demographics

Customer Cohort ID _____

clara^{T} Project ID (ADXYYXXX) ADX_____

Total No. of Samples _____

Date Samples Received (DD/MMM/YYYY) e.g. 01 JAN 2018 _____

Histology of Primary Disease _____

Site of Collection Tick as appropriate — Primary ☐ Metastatic ☐

No. of Samples _____ _____

Sample Format Tick as appropriate — FFPE ☐ FF ☐ Blood ☐ Cell Lines ☐

No. of Samples _____ _____ _____ _____

Client Contact: _____

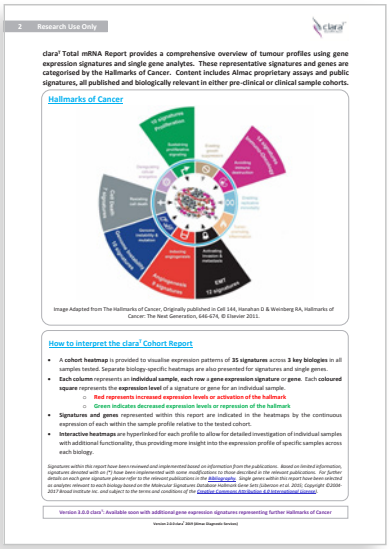
Company/Institute: _____

Customer Support - If you require any further information or assistance please contact: Almac Diagnostic Services clara^{T} Customer Support at +44 (0) 28 383 553 7575 (09:00-17:00 GMT, 7 days per week) or clarasupport@almacgroup.com

Research Use Only: The information provided within this report should not be used for diagnostic or prognostic purposes, including predicting responsiveness to a particular therapy.

Version 2.0.0 clara^{T} 2019 (Almac Diagnostic Services)

ALMAC


2 Research Use Only

clara^{T} Total mRNA Report provides a comprehensive overview of tumour profiles using gene expression signatures and single gene analytes. These representative signatures and genes are categorised by the Hallmarks of Cancer. Content includes Almac proprietary assays and public signatures, all published and biologically relevant in either pre-clinical or clinical sample cohorts.

Hallmarks of Cancer

Image Adapted from The Hallmarks of Cancer, Originally published in Cell 144, Hanahan D & Weinberg RA, Hallmarks of Cancer: The Next Generation, 646-674, © Elsevier 2011.

How to interpret the clara^{T} Cohort Report

- A **cohort heatmap** is provided to visualise expression patterns of **35 signatures** across **3 key biologies** in all samples tested. Separate biology-specific heatmaps are also presented for signatures and single genes.
- **Each column** represents an **individual sample**, **each row** a **gene expression signature** or **gene**. Each **coloured square** represents the **expression level** of a signature or gene for an individual sample.
  - **Red represents increased expression levels or activation of the hallmark**
  - **Green indicates decreased expression levels or repression of the hallmark**
- **Signatures and genes** represented within this report are indicated in the heatmaps by the continuous expression of each within the sample profile relative to the tested cohort.
- **Interactive heatmaps** are hyperlinked for each profile to allow for detailed investigation of individual samples with additional functionality, thus providing more insight into the expression profile of specific samples across each biology.

Signatures within this report have been reviewed and implemented based on information from the publications. Based on limited information, signatures denoted with an (*) have been implemented with some modifications to those described in the relevant publications. For further details on each gene signature please refer to the relevant publications in the Bibliography. Single genes within this report have been selected as analytes relevant to each biology based on the Molecular Signatures Database Hallmark Gene Sets (Liberzon et al. 2015). Copyright ©2006-2017 Broad Institute Inc. and subject to the terms and conditions of the Creative Commons Attribution 4.0 International License).

Version 2.0.0 clara^{T} 2019 (Almac Diagnostic Services) Available soon with additional gene expression signatures representing further Hallmarks of Cancer

Includes an interactive heat map

Dendrogram for clustering interpretation

Green indicates lower expression or repression

Red indicates increased expression or activation

Includes supplementary files with summarised scores for all signatures

Each row represents a signature

Each column represents a sample

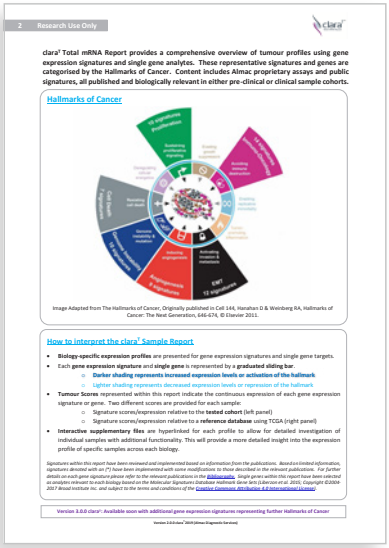
clara^{T} Sample Report:

The **clara^{T} Sample Report** gives greater insight into an individual sample and allows more detailed investigation of expression levels across signatures and single gene targets within a particular Hallmark of Cancer.

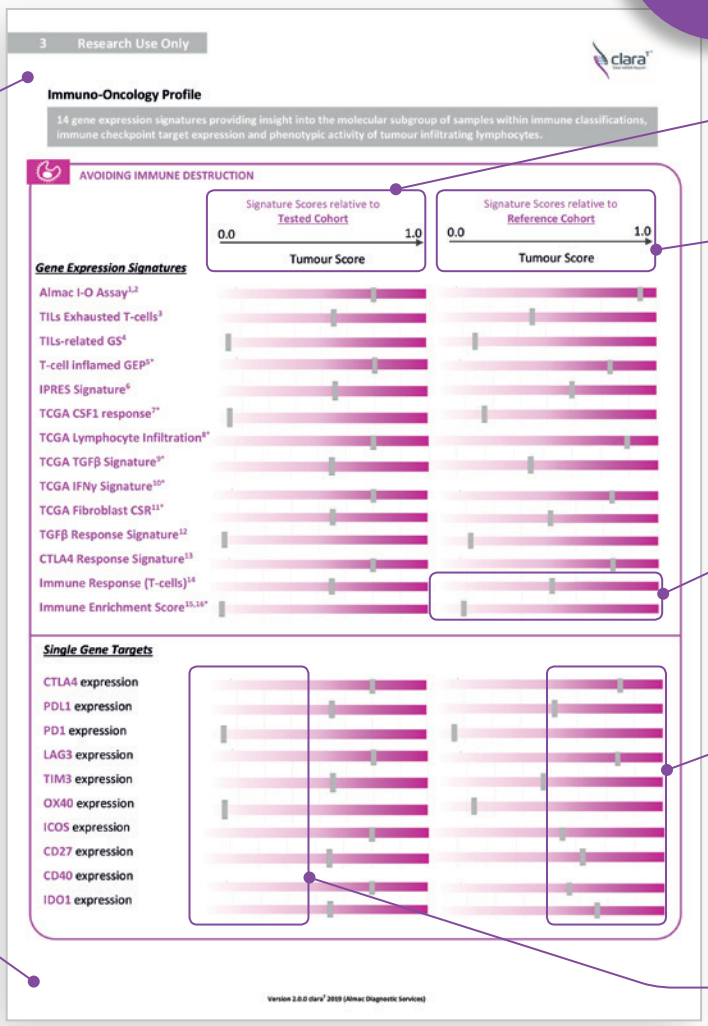
Interactive supplementary files are also included in the report and are hyperlinked within each profile for additional data functionality.

Advantages of the clara^{T} Sample Report:

- Determine the biological profile of your sample relative to the full cohort
- Define the underlying biology of your sample relative to a reference database
- Identify the most relevant gene expression signature / biology for your sample
- Identify key pathways of activity or repression in individual samples



Immuno-Oncology Example



Continuous signature scores/expression relative to the tested cohort

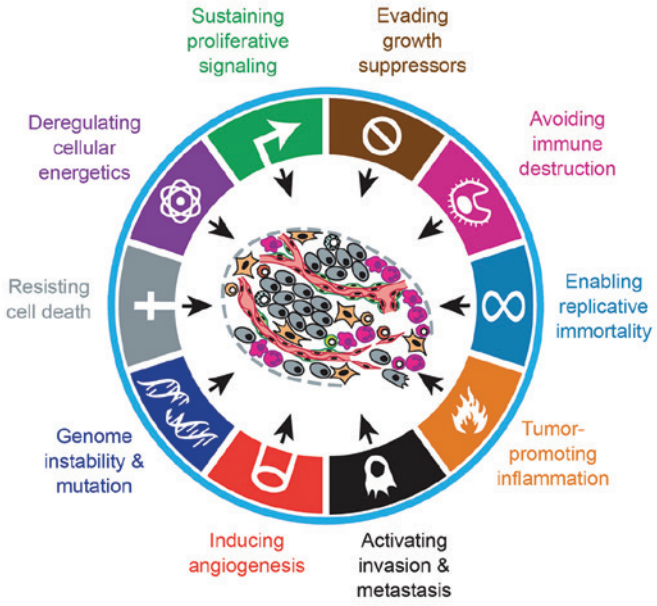
Continuous signature scores/expression relative to a reference database (TCGA)

Signature & single gene expression represented by graduated sliding bars

Darker shading represents increased expression or activation

Lighter shading represents decreased expression or repression

Hallmarks of Cancer:



clara^{T} Hallmarks Covered:

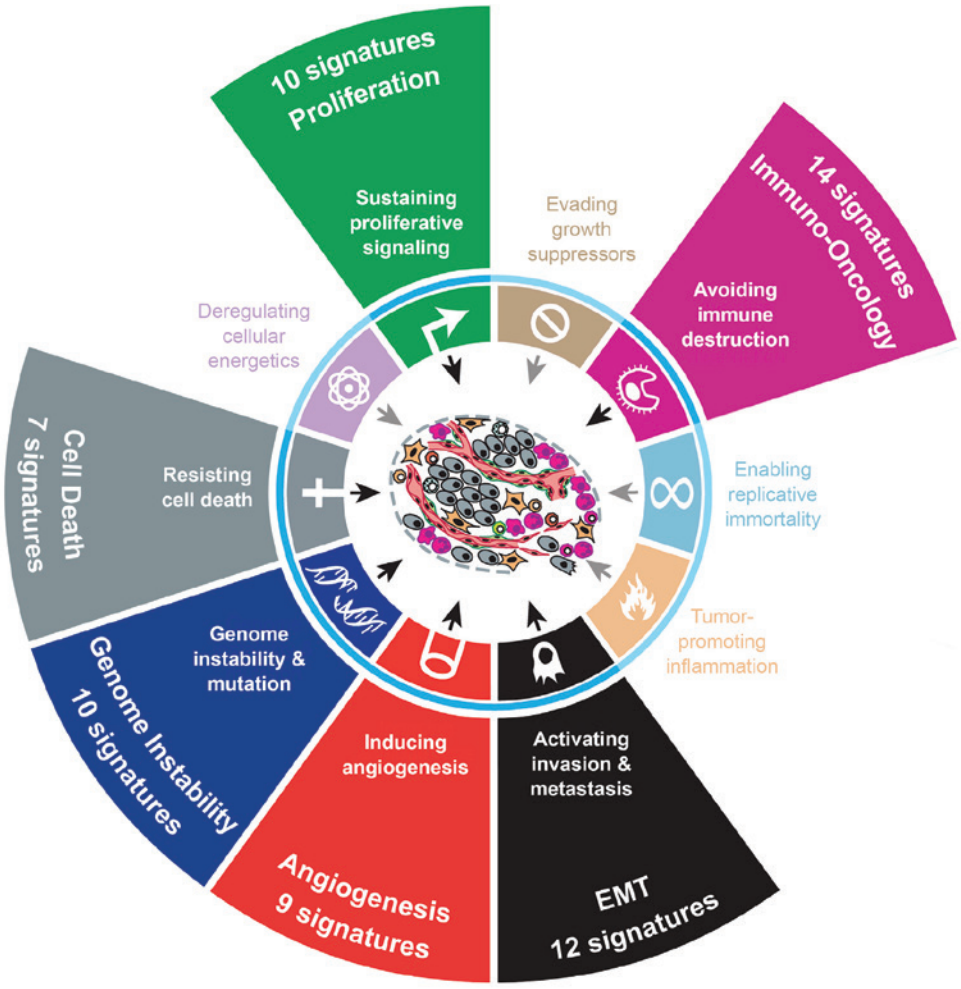


Image adapted from The Hallmarks of Cancer. Originally published in Cell 144, Hanahan D & Weinberg RA, Hallmarks of Cancer: The Next Generation, 646-674, © 2011. With permission from Elsevier.

clara^{T} - Utilising the Hallmarks of Cancer:

First conceptualised by Douglas Hanahan and Robert Weinberg in 2000 and subsequently updated in 2011, the **Hallmarks of Cancer** have become a paradigm within modern cancer research. The hallmarks help explain the complexity of cancer cells and describe the processes that occur allowing cancer cells to proliferate and grow if unchecked.

The clara^{T} report utilises the Hallmarks of Cancer concept of targetable biologies to help facilitate biomarker discovery. clara^{T} embodies the tenets set out by the authors, intelligently simplifying the complex biologies of cancer within key hallmarks.

clara^{T} content:

Immuno-Oncology

14 signatures

- Almac I-O Assay
- 5 x TCGA Subgroups
- 2 x TILs Signatures
- 2 x Immune Resistance Signatures
- 1 x T-cell Signature
- 1 x IFNγ Signature
- 1 x TGFβ Signature
- 1 x Immune Enrichment Score

EMT

12 signatures

- Almac EMT Assay
- 5 x EMT Pan-Can Signatures
- 2 x Stromal Signatures
- 1 x MAPK Activity
- 1 x Mesenchymal Subgroup
- 1 x MEK Functional
- 1 x EMT Enrichment Score

Angiogenesis

9 signatures

- Almac Angio Assay
- 4 x Angio Subgroup
- 1 x Hypoxia Signature
- 1 x Vascular Proliferation Signature
- 1 x Angio Predictive Signature
- 1 x Angio Enrichment Score

Genome Instability

10 signatures

- Almac DNA Damage Assay
- 2 x BRCA Signatures
- 2 x DDR Signatures
- 2 x Chromosomal Instability Signatures
- 1 x HRD Signature
- 1 x MSI Signature
- 1 x DNA Damage Enrichment Score

Proliferation

10 signatures

- 2 x HER2 Signatures
- 2 x EGFR Signatures
- 2 x MAPK Activity
- 1 x KRAS Signature
- 1 x MYC Activity
- 1 x STAT3 Signature
- 1 x PI3K/AKT Enrichment Score

Cell Death

7 signatures

- 2 x TNFα Signatures
- 1 x TP53 Signature
- 1 x TRAIL Activity
- 1 x Apoptosis Pathway Signature
- 1 x Autophagy Pathway Signature
- 1 x Apoptosis Enrichment Score

For further details on these signatures refer to the clara^{T} Fact Sheet.

clara^{T} Report – Facts:

- **6 key biologies**
- **62** gene expression signatures
- **60** drug targets
- **3,952 single genes** relevant to content

clara^{T} Report – Future:

Almac will continue to expand the clara^{T} report by developing content to eventually cover **all 10 Hallmarks of Cancer**.

How to order clara^{T}:

Call | Speak to a Business Development Manager | Contact us online

- Go to the Almac Diagnostic Services **website** www.almacgroup.com/diagnostics
- Click on the **clara^{T} page** and fill in the **contact us** form
- One of our **Business Development Managers will be in touch** to discuss your requirements
- Almac Diagnostic Services will send a **quotation based on your specific requirements**
- If proceeding, **complete the scope of work and sample manifest, sign the T&Cs** and return to claratsupport@almacgroup.com
- **A primary point of contact will be assigned to you for the duration of your project**

About Almac Diagnostic Services:

Almac Diagnostic Services is a global stratified medicine company specialising in biomarker driven clinical trials, with laboratories in the UK, USA and a partner laboratory based in China.

As part of the wider Almac Group, we are a stable, privately owned business that is growing globally in line with increased customer demand. Our diagnostic experience spans oncology, immunology, CNS and infective diseases.

Want to know more about how clara^{T} can help your biomarker discovery and translational research?

almacgroup.com

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