7 November 2018

HARDMAN&CO.

THIS DOCUMENT IS NOT AVAILABLE FOR DISTRIBUTION TO 'U.S. PERSONS', NOR TO PARTIES WHO ARE NOT CONSIDERED 'RELEVANT PERSONS' IN THE UNITED KINGDOM, NOR SHOULD IT BE TAKEN, TRANSMITTED OR DISTRIBUTED, DIRECTLY OR INDIRECTLY, TO EITHER OF THESE CATEGORIES. THIS DOCUMENT HAS BEEN FURNISHED TO YOU SOLELY FOR YOUR INFORMATION. SEE PAGES 3-4 FOR FURTHER DETAILS.

# CHRONIX BIOMEDICAL

## Monitoring treatment, improving outcomes

**Chronix Biomedical is a privately-owned biotechnology company specialising in liquid biopsies for monitoring the effectiveness of cancer drugs, including immunotherapies, in real time. It also has a marketed product for detecting organ rejection, in as little as hours, following transplant. The primary benefit of these products, marketed under the TheraSure brand, is in improving patient outcomes by assisting clinical decision making. A favourable pricing model, aided by Chronix's asset-light structure, provides an excellent commercial profile. Chronix is seeking a funding round of $10-30m to support further commercialisation.**

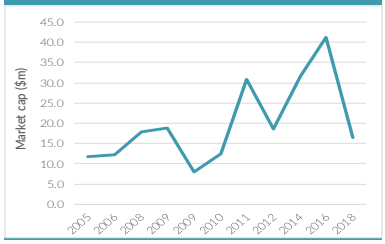
- **Strategy:** Chronix operates primarily in the transplant and cancer therapy monitoring markets. The TheraSure brand was recently launched in Europe. With little direct competition, it is harnessing its first-mover advantage initially in Europe, then in the US, by out-licensing its tests to accredited laboratories.
- **Improving outcomes:** TheraSure offers significant health economic advantages through improving patient outcomes and via its reasonable pricing model. The technology provides early evidence of immunotherapy or transplant failure, informing real-time clinical decision making, and a reduced burden on payers.
- **Valuation:** Since incorporation, Chronix has raised a total of $44.6m through a series of funding rounds at an average price of $0.27 per share. The last round provided the funds, and was concluded, prior to both the signing of an exclusive 15-year commercial license with a large German laboratory chain, which has an NPV of at least $92m, and a material increase in the number of patents granted. Therefore, the pre-money valuation is prior to both of these material events.
- **Risks:** Investments in private, early-stage companies carry a significant risk. Patent robustness, the regulatory and reimbursement environment, and competition in a crowded market are all factors that could impede Chronix's progress.
- **Investment summary:** Chronix is looking to raise $10-30m in a pre-IPO funding round to take it through the early stages of commercialisation with Amedes, to undertake clinical trials to enhance its regulatory programmes, and to maintain/strengthen its patent position. There is a large and growing demand for accurate cancer therapy monitoring, for which Chronix has the IP.

**Financial summary and valuation**

| Year-end Dec ($m) | 2015 | 2016 | 2017 | 2018E | 2019E | 2020E |
|---|---|---|---|---|---|---|
| Sales | 0.00 | 0.00 | 0.00 | 0.82 | 3.48 | 5.67 |
| EBITDA | -3.67 | -4.47 | -3.33 | -2.75 | -6.10 | -3.69 |
| Underlying EBIT | -3.81 | -4.53 | -3.36 | -2.78 | -6.13 | -3.75 |
| Reported EBIT | -3.81 | -4.53 | -3.36 | -2.78 | -6.13 | -3.75 |
| Underlying PBT | -3.88 | -4.54 | -3.47 | -2.85 | -6.08 | -3.58 |
| Statutory PBT | -3.88 | -4.75 | -3.47 | -2.85 | -6.08 | -3.58 |
| Underlying EPS ($) | -0.04 | -0.02 | -0.03 | -0.02 | -0.03 | -0.02 |
| Statutory EPS ($) | -0.03 | -0.02 | -0.02 | -0.01 | -0.02 | -0.01 |
| Net (debt)/cash | 1.16 | 0.53 | -0.97 | 5.05 | 16.96 | 12.31 |
| Capital increases | 4.11 | 2.92 | 2.21 | 3.90 | 20.00 | 0.00 |
| EV/sales (x) | - | - | - | 13.9 | 3.3 | 2.0 |
| EV/EBITDA (x) | - | - | - | - | -1.9 | -3.1 |

*Source: Hardman & Co Life Sciences Research*

**Pharmaceuticals & Biotechnology**




*Source: Eikon Thomson Reuters*

**Market data**

| | |
|---|---|
| EPIC/TKR | - |
| Last funding | 2018 |
| Average price | $0.27 |
| Shares in issue | 164.7m |
| Capitalisation | $44.5m |
| Pre-IPO financing target | $10-30m |
| Pre-money valuation | ca.$60m |

*Source: Hardman & Co Life Sciences Research*

**Description**

Chronix Biomedical is a private biotech company that specialises in liquid biopsies for assessing the effectiveness of cancer therapies, and the detection of organ rejection after transplantation. It is commercialising its products through specialist clinical testing laboratories.

**Company information**

| | |
|---|---|
| CEO | Prof. Ekkehard Schütz |
| CFO | John DiPietro |
| Chairman | David Mackenzie |
| | +1 408 960 2307 |
| | www.chronixbiomedical.com |

**Key shareholders**

| | |
|---|---|
| Directors | 23.9% |
| Management | 2.3% |
| Others | 73.8% |

**Diary**

| | |
|---|---|
| 2018-2019 | Funding round |

**Analysts**


| | |
|---|---|
| Martin Hall | 020 7194 7632 |
| | mh@hardmanandco.com |
| Dorothea Hill | 020 7194 7626 |
| | dmh@hardmanandco.com |
| Grégoire Pavé | 020 7194 7628 |
| | gp@hardmanandco.com |

# Table of contents

# IMPORTANT INFORMATION

DUE TO LEGAL RESTRICTIONS, THE INFORMATION IN THIS DOCUMENT IS NOT AVAILABLE TO ANY PERSON WHO IS A "U.S. PERSON" (AS DEFINED BELOW) OR TO ANY PERSON WHO IS PHYSICALLY PRESENT IN THE UNITED STATES, AND IT IS AVAILABLE ONLY TO PERSONS WHO ARE "RELEVANT PERSONS" (AS DEFINED BELOW) FOR U.K. REGULATORY PURPOSES.

A "U.S. PERSON" IS:

- ANY NATURAL PERSON RESIDENT IN THE UNITED STATES;
- ANY PARTNERSHIP OR CORPORATION ORGANISED OR INCORPORATED UNDER THE LAWS OF THE UNITED STATES;
- ANY ESTATE OF WHICH ANY EXECUTOR OR ADMINISTRATOR IS A "U.S. PERSON";
- ANY TRUST OF WHICH ANY TRUSTEE IS A "U.S. PERSON";
- ANY AGENCY OR BRANCH OF A FOREIGN ENTITY LOCATED IN THE UNITED STATES;
- ANY NON-DISCRETIONARY ACCOUNT OR SIMILAR ACCOUNT (OTHER THAN AN ESTATE OR TRUST) HELD BY A DEALER OR OTHER FIDUCIARY FOR THE BENEFIT OR ACCOUNT OF A "U.S. PERSON";
- ANY DISCRETIONARY ACCOUNT OR SIMILAR ACCOUNT (OTHER THAN AN ESTATE OR TRUST) HELD BY A DEALER OR OTHER FIDUCIARY ORGANISED, INCORPORATED, OR (IF AN INDIVIDUAL) RESIDENT IN THE UNITED STATES; AND
- ANY PARTNERSHIP OR CORPORATION IF:
  - ORGANISED OR INCORPORATED UNDER THE LAWS OF ANY FOREIGN JURISDICTION; AND
  - FORMED BY A "U.S. PERSON" PRINCIPALLY FOR THE PURPOSE OF INVESTING IN SECURITIES NOT REGISTERED UNDER THE U.S. SECURITIES ACT, UNLESS IT IS ORGANISED OR INCORPORATED, AND OWNED, BY ACCREDITED INVESTORS (AS DEFINED IN THE RULES OF THE U.S. SECURITIES AND EXCHANGE COMMISSION) WHO ARE NOT NATURAL PERSONS, ESTATES OR TRUSTS.

"RELEVANT PERSONS" ARE (I) PERSONS WHO ARE OUTSIDE THE UNITED KINGDOM OR (II) INVESTMENT PROFESSIONALS FALLING WITHIN ARTICLE 19(5) OF THE FINANCIAL SERVICES AND MARKETS ACT 2000 (FINANCIAL PROMOTION) ORDER 2005 (THE "ORDER") OR (III) HIGH NET WORTH COMPANIES, AND OTHER PERSONS TO WHOM IT MAY LAWFULLY BE COMMUNICATED, FALLING WITHIN ARTICLE 49(2) (A) TO (D) OF THE ORDER. THE SECURITIES OF THE COMPANY ARE ONLY AVAILABLE TO, AND ANY INVITATION, OFFER OR AGREEMENT TO SUBSCRIBE, PURCHASE OR OTHERWISE ACQUIRE SUCH SECURITIES WILL BE ENGAGED IN ONLY WITH, RELEVANT PERSONS. ANY PERSON WHO IS NOT A RELEVANT PERSON SHOULD NOT ACCESS, OR SEEK TO ACT OR RELY ON, THIS REPORT OR ANY OF ITS CONTENTS.

THIS DOCUMENT SHOULD NOT BE TAKEN, TRANSMITTED OR DISTRIBUTED, DIRECTLY OR INDIRECTLY, TO "U.S. PERSONS" AS DEFINED ABOVE NOR TO PARTIES THAT ARE NOT "RELEVANT PERSONS" AS DEFINED ABOVE. IN READING THIS DOCUMENT THE READERS ALSO ACKNOWLEDGE THAT THEY HAVE READ AND UNDERSTOOD THE NOTICES SET FORTH ABOVE AND THE DISCLAIMERS CONTAINED IN THE DOCUMENT.

IF YOU ARE NOT A 'RELEVANT PERSON' OR YOU ARE A "U.S. PERSON", YOU SHOULD NOT HAVE RECEIVED OR ACCESSED THIS DOCUMENT AND ACCORDINGLY SHOULD RETURN THIS DOCUMENT AS SOON AS POSSIBLE AND TAKE NO FURTHER ACTION. ANY INVESTMENT OR INVESTMENT ACTIVITY TO WHICH THIS DOCUMENT RELATES IS ONLY AVAILABLE TO "RELEVANT PERSONS". BY ACCEPTING RECEIPT OF THIS DOCUMENT, EACH RECIPIENT IS DEEMED TO CONFIRM, REPRESENT AND WARRANT TO HARDMAN & CO THAT IT IS A "RELEVANT PERSON" AND THAT IT IS NOT A "US PERSON", AND ACCORDINGLY A PERSON TO WHOM THIS DOCUMENT CAN BE LAWFULLY COMMUNICATED.

THIS DOCUMENT IS BEING FURNISHED TO YOU SOLELY FOR YOUR INFORMATION ON A CONFIDENTIAL BASIS AND MAY NOT BE REPRODUCED, REDISTRIBUTED OR PASSED ON, IN WHOLE OR IN PART, TO ANY OTHER PERSON. IN PARTICULAR, THE DISTRIBUTION OF THIS DOCUMENT IN OTHER JURISDICTIONS MAY BE RESTRICTED BY LAW AND PERSONS INTO WHOSE POSSESSION THIS DOCUMENT COMES SHOULD INFORM THEMSELVES ABOUT, AND

OBSERVE, ANY SUCH RESTRICTION. ANY FAILURE TO COMPLY WITH THESE RESTRICTIONS MAY CONSTITUTE A VIOLATION OF THE LAWS OF ANY SUCH OTHER JURISDICTION. BY ACCEPTING THIS REPORT, YOU AGREE TO BE BOUND BY THE FOREGOING LIMITATIONS.

THIS DOCUMENT DOES NOT CONSTITUTE OR FORM PART OF, AND SHOULD NOT BE CONSTRUED AS, AN OFFER OR INVITATION TO SUBSCRIBE FOR OR PURCHASE ANY SECURITIES, AND NEITHER THIS DOCUMENT NOR ANYTHING CONTAINED HEREIN SHALL FORM THE BASIS OF OR BE RELIED ON IN CONNECTION WITH OR ACT AS AN INDUCEMENT TO ENTER INTO ANY CONTRACT OR COMMITMENT WHATSOEVER. THIS DOCUMENT HAS NOT BEEN PUBLISHED GENERALLY AND HAS ONLY BEEN MADE AVAILABLE TO PROFESSIONAL INVESTORS. ANY DECISION TO SUBSCRIBE FOR OR PURCHASE SECURITIES IN ANY OFFERING MUST BE MADE SOLELY ON THE BASIS OF THE RECIPIENT'S OWN INVESTIGATION AND DUE DILIGENCE AND ON THE INFORMATION AND OFFERING DOCUMENTATION ISSUED IN CONNECTION WITH SUCH OFFERING AND NOT ON THE BASIS OF THE CONTENTS OF THIS DOCUMENT.

FOR THE PURPOSE OF UK LAWS, RULES AND REGULATIONS, THIS DOCUMENT IS CLASSIFIED AS BEING A NON-INDEPENDENT MARKETING COMMUNICATION. IT HAS NOT BEEN PREPARED IN ACCORDANCE WITH LEGAL REQUIREMENTS DESIGNED TO PROMOTE THE INDEPENDENCE OF INVESTMENT RESEARCH AND IS NOT SUBJECT TO ANY PROHIBITION ON DEALING AHEAD OF THE DISSEMINATION OF INVESTMENT RESEARCH.

THIS DOCUMENT HAS BEEN PRODUCED INDEPENDENTLY OF CHRONIX BIOMEDICAL, INC. (THE "COMPANY") AND ITS SHAREHOLDERS, AND ANY FORECASTS, OPINIONS AND EXPECTATIONS CONTAINED HEREIN ARE ENTIRELY THOSE OF HARDMAN & CO AND ARE GIVEN AS PART OF ITS NORMAL RESEARCH ACTIVITY AND SHOULD NOT BE RELIED UPON AS HAVING BEEN AUTHORISED OR APPROVED BY ANY OTHER PERSON. HARDMAN & CO HAS NO AUTHORITY WHATSOEVER TO MAKE ANY REPRESENTATION OR WARRANTY ON BEHALF OF THE COMPANY, ITS SHAREHOLDERS, ANY OF ITS ADVISERS, OR ANY OTHER PERSON IN CONNECTION THEREWITH. WHILE ALL REASONABLE CARE HAS BEEN TAKEN TO ENSURE THAT THE FACTS STATED HEREIN ARE ACCURATE AND THAT THE PROJECTIONS, FORECASTS, ESTIMATES, OPINIONS AND EXPECTATIONS CONTAINED HEREIN ARE FAIR AND REASONABLE, HARDMAN & CO HAS NOT VERIFIED THE CONTENTS HEREOF AND ACCORDINGLY NONE OF HARDMAN & CO, THE COMPANY, ITS SHAREHOLDERS, ANY ADVISERS TO THE COMPANY OR ITS SHAREHOLDERS OR ANY OTHER PERSON IN CONNECTION THEREWITH NOR ANY OF THEIR RESPECTIVE DIRECTORS, OFFICERS OR EMPLOYEES, SHALL BE IN ANY WAY RESPONSIBLE FOR THE CONTENTS HEREOF AND NO RELIANCE SHOULD BE PLACED ON THE ACCURACY, FAIRNESS, OR COMPLETENESS OF THE INFORMATION CONTAINED IN THIS DOCUMENT. NO PERSON ACCEPTS ANY LIABILITY WHATSOEVER FOR ANY LOSS HOWSOEVER ARISING FROM THE USE OF THIS DOCUMENT OR OF ITS CONTENTS OR OTHERWISE ARISING IN CONNECTION THEREWITH.

NOTHING IN THIS DOCUMENT IS, OR SHOULD BE RELIED ON AS A PROMISE OR REPRESENTATION AS TO THE FUTURE. THIS DOCUMENT CONTAINS FORWARD-LOOKING STATEMENTS, WHICH REFLECT THE VIEWS OF HARDMAN & CO WITH RESPECT TO, AMONG OTHER THINGS, THE COMPANY'S OPERATIONS. THESE FORWARD-LOOKING STATEMENTS ARE IDENTIFIED BY THE USE OF WORDS SUCH AS "BELIEVE", "EXPECT", "POTENTIAL", "CONTINUE", "MAY", "WILL", "SHOULD", "SEEK", "APPROXIMATELY", "PREDICT", "INTEND", "PLAN", "ESTIMATE", "ANTICIPATE" OR OTHER COMPARABLE WORDS. THESE FORWARD-LOOKING STATEMENTS ARE SUBJECT TO VARIOUS RISKS, UNCERTAINTIES AND ASSUMPTIONS. ACCORDINGLY, THERE ARE, OR WILL BE, IMPORTANT FACTORS THAT COULD CAUSE ACTUAL OUTCOMES OR RESULTS TO DIFFER MATERIALLY FROM THOSE INDICATED IN THESE STATEMENTS. SHOULD ANY ASSUMPTIONS UNDERLYING THE FORWARD-LOOKING STATEMENTS CONTAINED IN THIS DOCUMENT PROVE TO BE INCORRECT, THE ACTUAL OUTCOME OR RESULTS MAY DIFFER MATERIALLY FROM OUTCOMES OR RESULTS PROJECTED IN THESE STATEMENTS. HARDMAN & CO IS UNDER NO OBLIGATION TO UPDATE OR REVIEW ANY FORWARD-LOOKING STATEMENT, WHETHER AS A RESULT OF NEW INFORMATION, FUTURE DEVELOPMENTS OR OTHERWISE, EXCEPT AS REQUIRED BY APPLICABLE LAW OR REGULATION.

# Executive summary

## Company overview

Chronix Biomedical is a privately-owned biotechnology company specialising in liquid biopsies for non-invasive monitoring of the effectiveness of cancer therapies and transplants. Founded in 1997, Chronix is headquartered in California, US, but has its R&D headquarters in Gottingen, Germany, where its first commercial partnership was recently signed. Having launched its first products in Europe, it is seeking a $10-30m financing to support additional clinical studies and broader global commercialisation.

## Chronix technology

The company has two commercially available liquid biopsy tests under the TheraSure brand – the CNI MONITOR for cancer and the Transplant MONITOR – in addition to a pipeline of cancer-specific second opinion and recurrence monitoring products. Its proprietary algorithm for quantification of genome-wide copy variation in DNA from the bloodstream is an elegant solution to some of the complexities hindering competing technologies. Chronix's technology is protected by a broad suite of patents.

## Market opportunity

The molecular *in vitro* diagnostics market for cancer diagnosis, monitoring, and treatment selection is forecast to be in excess of $2.5bn in 2018 and is growing at ca.20% p.a. Chronix has excellent technology with few direct competitors, and its tests are >86% accurate, greater than both conventional and competing products. Conservative forecasts indicate revenue of about $25m within five years. Depending on commercial success, particularly in the US, the company could achieve significant market share by 2025.

## Commercial strategy

Chronix is harnessing the first-mover advantage afforded by its unique technology to achieve significant revenue first in Europe, where there are fewer market barriers, and later in the US, where the regulatory and reimbursement environment is significantly more complex. Revenues will be driven by high-volume sales of reasonably priced tests that have clear health economic advantages for monitoring – they allow early detection of treatment response, improving outcomes and reducing payer burden.

The mid-term activities of the company will be dictated by the quantum of funds raised in the next round. $5m is required to finish existing trials and support the initial commercial programme and a further $15m is needed to expand the trial programme and support the commercial rollout into more territories. Any move towards cancer screening tests would require considerably greater funding.

## Financial summary

To date, Chronix has raised a total of $44.6m through a series of funding rounds at an average price of $0.27 per share. The most recent, during 2017-18, was the largest, resulting in gross new funds of $6.2m. The company is seeking to raise an additional $10-30m in a pre-IPO funding round to take the company through the early stages of commercialisation with amedes-group (Amedes), to finish/undertake some supportive clinical trials to enhance its regulatory programmes, and to maintain and strengthen its patent position.

## Valuation

The last round of funding began 15 months prior to the signing of its first commercial license agreement, which resulted in Chronix having sufficient funds to negotiate the agreement. Subsequent to this round, Chronix was granted greater patent protection (nine patents granted and allowed in EU and North America) and signed the important exclusive commercial deal for 15 years with a large German specialist clinical laboratory group, which has an NPV of at least $92m, based on a minimum annual number of tests. Neither of these material events were reflected in the valuation of the 2017-18 funding round.

### *Peer group comparisons*

- The average EV of a group of UK peers working in the field of *in vitro* diagnostics (IVD) is £76.2m (range £47.1m-178.4m), which is 2.5x the EV of Chronix based on the average of its funding rounds.
- On the same basis, the relative EV of a group of global peers with IVD products is in the range 1.4x to 62.1x, with an average of 25.0x. The more highly rated tend to be companies with products that are already being commercialised.
- In addition to the cancer prospect, there is one company with a commercial liquid biopsy product for transplants. CareDx has an EV of $999m and is trading on a prospective EV/sales ratio of 15.4x

### *M&A activity*

The strategy of the large global players in the field of diagnostics and clinical laboratory testing has been to let the small companies take all the development risk and then to acquire the company/technology when it has been de-risked and started commercialisation. Prices paid have represented a handsome return for investors, with an average EV/sales ratio of 19.2x being paid by the acquiring company.

## Investment conclusion

Chronix is at a very interesting stage. Its leading products have been largely de-risked and are on the cusp of commercialisation, as evidenced by the extremely attractive deal signed with Amedes for the oncology diagnostic, TheraSure CNI MONITOR, in selected territories in Europe. Other deals are under discussion and likely to follow shortly. Also, while TheraSure Transplant MONITOR is addressing a much smaller market, Chronix's only competitor is valued at $999m, or 15.4x prospective sales.

Our UK and global peer group analyses suggest that there is considerable upside potential in the valuation of Chronix, especially given that it has invested nearly $45m to get the company where it is today. Therefore, an investment is underpinned by a de-risked proposition for unique technology, a commercial deal for parts of Europe, and a strong executive management team. It ticks all the boxes!

**Investor summary**

| Investment criteria | Status | Comment | Page |
|---|---|---|---|
| Strong intellectual property | ✓ | Oncology covered; need to strengthen US IP for transplant | 18 |
| Large market potential | ✓ | Oncology IVD $2.5bn in 2018 | 23 |
| Products with competitive advantage | ✓ | Only group with CNI technology | 8 |
| Defined regulatory pathway | ✓ | LDT initially, then CE marking and 510(K) | 20 |
| USP/competitive landscape | ✓ | CNI/multiple small competitors | 16 |
| Licensing deals | ✓ | Attractive EU deal with Amedes | 19 |
| Product sales | ✓ | Starting in fiscal 2018 | 27 |
| Potential to expand product range | ✓ | Targeting of specific cancers | 9, 30 |
| Potential to achieve exit in 5 years | ✓ | High prices for de-risked assets | 30 |

*Source: Hardman & Co Life Sciences Research*

# Chronix: disease surveillance

## Chronix Biomedical – overview

Specialist liquid biopsies

Source: Chronix Biomedical

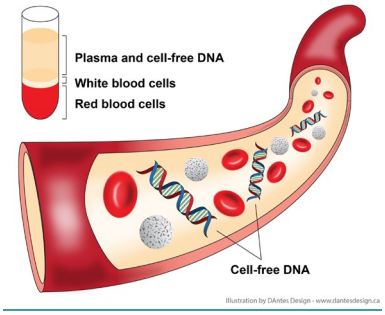
Chronix Biomedical is a private biotechnology company that was founded in 1997. It is headquartered in California, US, but has its R&D headquarters in Gottingen, Germany, where its first commercial partnership was recently signed. Chronix specialises in monitoring the success of cancer treatment and organ transplant using its proprietary algorithm for quantification of genetic copy number variation, and its digital PCR methodology, respectively, using only patient blood samples.

The company has two commercially available tests under the TheraSure brand – the CNI MONITOR for cancer and the Transplant MONITOR – in addition to a pipeline of cancer-specific second opinion and recurrence monitoring products. TheraSure tests are 'liquid biopsies', so called because they allow molecular characterisation of disease without the need for surgical extraction of cells or tissue. The main advantage of Chronix's technology over that of competitors' is its specificity, which is above 86%. Its primary advantages over conventional methods include:

- Improved patient outcomes
- Reduced burden on healthcare payers
- Pain-free and real-time monitoring for clinical decision making
- Earlier assessment of response to treatment or transplant

## TheraSure™ CNI MONITOR

Cell-free DNA




Source: Reproduced with kind permission from DAntes Design, Toronto, Canada

### Biological premise

In brief, cell-free DNA (cfDNA) is fragments of naked DNA circulating in the blood stream which, in cancer patients, is thought to be mostly derived from tumour cells that have undergone apoptosis (for more, see 'Liquid Biopsy Industry' section, page 8). A characteristic of many cancer cells is a higher or lower amount of genetic material than normal, and by extracting cfDNA from patients' blood samples and quantifying the genetic material present across the whole genome, the presence of cancer may be identified. Chronix's proprietary algorithm calculates a statistical measure of copy number variation relative to healthy controls, called a 'copy number instability' (CNI) score. When calculated at different time points during and after treatment, changes in CNI score can be used as a surrogate of changes in tumour load/aggressiveness. This allows doctors to monitor the success or failure of therapy, and to change or continue with a regimen as needed.

### Primary advantages

The advantages of the TheraSure CNI MONITOR include improved patient experience, clinical outcome, and burden on payers – see the table below – in contrast with the standard-of-care, RECIST (Response Evaluation in Solid Tumours). RECIST criteria use radiological imaging to follow changes in tumour load and are employed in most clinical trials that evaluate response to tumour therapy. Imaging, however, can have limited sensitivity and is time consuming and expensive to perform. In addition, since most chemotherapies are given in multiple cycles over more than three months, repeated scanning can be distressing to patients and cause side effects. The analytical and clinical validity of TheraSure has been demonstrated in two fully published clinical studies, with additional studies currently ongoing.

| Clinical and economic advantages | | |
|---|---|---|
| **Comparator** | **TheraSure CNI monitor** | |
| Other DNA-based liquid biopsies | More accurate | ✓ |
| Standard-of-care | Earlier detection of response and recurrence | ✓ |
| Conventional tumour biopsy | Non-invasive | ✓ |
| Standard-of-care | Cheaper | ✓ |

*Source: Hardman & Co Life Sciences Research*

## Efficient and rapid turnaround

As the laboratory procedure is rapid, streamlined and CNI scoring is computational and automated, a TheraSure CNI MONITORING result can be obtained in as little as three days after a blood sample is taken in the clinic or hospital. The rate limiting step will always be the time taken for samples to be shipped to a sequencing facility, if there is none on site, as with any other DNA sequence-based procedure.

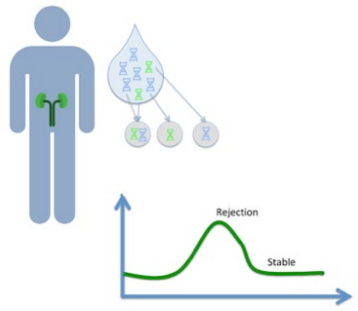
| Approximate timescale for processing one sample | | |
|---|---|---|
| **Site** | **Description** | **Approx. timescale** |
| 1 | Blood sample taken in clinical setting (usually 10ml) | Day 1 |
| 2 | Sample sent to third-party accredited laboratory for processing | Day 2 |
| | Blood centrifuged to separate plasma | Day 2 |
| | DNA extraction | Day 2 |
| | DNA library preparation and sequencing | Day 2/3 overnight |
| | DNA sequence reads enter Chronix analysis pipeline via internet | Day 3 |
| 3 | Bioinformatic analysis at Chronix laboratory | Day 3 |
| | CNI score derived and visual display produced | Day 3 |
| 4 | Clinical decision making | Day 3+ |

*Source: Hardman & Co Life Sciences Research*

CNI monitoring can be carried out as often as is required by the treating physician. In the studies completed to date, samples have been taken when most practical – when patients have come in to the clinic prior to the start of therapy cycles.

# TheraSure™ Transplant MONITOR

**TheraSure Transplant MONITOR**




*Source: Hardman & Co Life Sciences Research*

Like the CNI MONITOR, the TheraSure Transplant MONITOR is a DNA-based liquid biopsy. It uses a different technique, Chronix's proprietary digital droplet PCR methodology, to quantify the concentration of cfDNA that is attributable to the donor organ rather than to the patient – these can be distinguished on the basis of the genome sequence, which is unique to donor and recipient. The use of graft cfDNA (GcfDNA) as a marker of transplant rejection has been clinically validated by both Chronix and third parties; it is thought to increase in the bloodstream when cells of the transplant organ are killed by the immune system.

## Main advantages

There are at least one million organ transplant patients at any one time worldwide. While transplantation can be highly effective, the shortage of suitable donor organs makes it imperative to prevent rejection, to reduce the need for additional donor organs and to prolong graft survival. All patients are treated with immunosuppressive drugs to prevent rejection and are carefully monitored for toxicity. However, current post-transplant monitoring relies on biochemical tests that are unable to give an early indication of rejection or its severity. Suspected rejection must then be confirmed by tissue biopsy – side effects include pain, bleeding, and infection.

When compared to tissue biopsies and biochemical tests of organ function, the TheraSure Transplant MONITOR has clear advantages, validated in clinical studies:

- Earlier diagnosis of donor organ rejection
- Earlier clinical decision making – saving treatment costs and improving outcomes

- Avoiding unnecessary biopsies – reducing harm and distress to the patient

## Testing approach

As with the TheraSure CNI MONITOR, the transplant product has a fast turnaround time and is inexpensive and simple to perform. The straightforward workflow means that technology transfer to licensed laboratories is quick and easy, and the use of a PCR method means low cost of goods, reducing the economic burden for payers. On average, 20 to 30 tests are usually carried out per patient in the three years following transplant, or 50 to 60 over the lifespan of a transplant.

**TheraSure Transplant MONITOR**

| Time after transplant | Testing | Number tests in period per patient, year 1 | Approx. cumulative cost to payer per patient, year 1* |
|---|---|---|---|
| 1st month | Weekly | 4 | $1,380-1,800 |
| Next five months | Monthly | 5 | $3,105-4,050 |
| After six months | Quarterly | 2 | $3,795-4,950 |
| Clinical complications | As needed | | |

**Based one end-selling price per test in range $345-$450, of which we expect Chronix to receive 30%*
*Source: Chronix Biomedical, Hardman & Co Life Sciences Research*

# Pipeline products

In addition to the TheraSure CNI and Transplant MONITOR, Chronix is actively developing a pipeline of new cancer diagnostic and recurrence monitoring tests based on cfDNA. In the longer term, a CNI Screening product is being considered.

**Chronix pipeline**

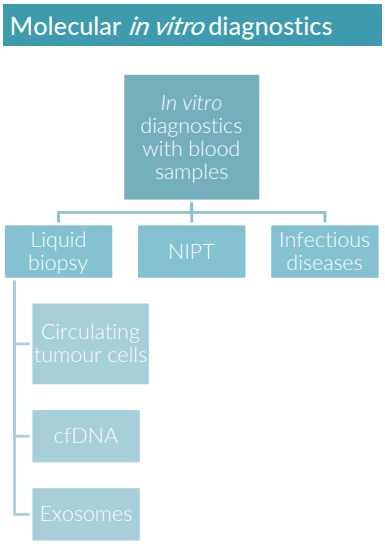
| Product | Purpose | Clinical potential | Development stage |
|---|---|---|---|
| CNI Second Opinion | Supplemental diagnostic test for prostate cancer | Reduce unnecessary tissue biopsies, particularly in false positive PSA* tests<br>Non-invasive serial testing for 'watchful waiting' | In clinical trials |
| | And for breast cancer | | In clinical trials |
| CNI MONITOR | Additional indication: for patients in remission | Early detection of cancer recurrence & cost saving through early treatment | |
| CNI Screen | Screening tests – cancers | Early detection of cancer in asymptomatic individuals | Funding required – capital-intensive trials |

**PSA=Prostate specific antigen*
*Source: arch/Chronix Biomedical*

## CNI screening: a future prospect

In the longer term, Chronix is planning to develop cancer screening tests. CNI scoring technology has potential advantages over other DNA-based liquid biopsies, such as SNPs, in screening because it has a higher specificity. However, clinical trials to develop and test the thresholds for CNI scores for screening would have to be very large (Chronix estimates >2,000 patients, plus a very large control group of >10,000), because screening is carried out in members of higher risk populations (e.g. general cancer risk identified) who have not been diagnosed with cancer, usually as part of national government initiatives, and as such it is imperative that screening tests are as specific as possible to avoid false positives. Such trials, therefore, would be cost intensive ($20-30m) and, as such, development of a screening test is not a current priority, unless adequate funding is procured.

# Liquid biopsy industry




*NIPT: Non-invasive prenatal testing*
*Source: Hardman & Co Research*

Since Chronix is a specialist liquid biopsy company, we focus on this segment of the *in vitro* molecular diagnostics market. Most tests in each of the three market segments are offered as either complete kits (specialist machines, plus specific consumables/reagents) or as proprietary laboratory developed tests (LDTs), which are carried out in a single laboratory. Chronix has developed its technology as LDTs.

## Background: monitoring and diagnosis

The liquid biopsy market is currently almost entirely geared towards the following applications in transplanted organs and in oncology:

- early patient diagnosis (following clinical presentation);
- monitoring response to therapy; and
- targeted/personalised therapy.

To our knowledge, there are few liquid biopsy tests approved for the screening of specific cancers; this area of the market is likely to grow dramatically in the coming decade, but the main hurdle is the expense and size of clinical trials needed for such an application. For example, Grail, a leading player, has invested >$1bn to date in genetic screening and is still without a commercial product.

The aim of screening is to diagnose disease prior to the onset of symptoms, usually within high-risk but healthy patients. This requires the tests to have extremely high specificity, for the avoidance of false positives. All tests produce false positives (they are not 100% specific) and false negatives (they are not 100% sensitive) and, therefore, depending on the procedure, the negatives of screening can outweigh the positives. For example, the Pap test is highly effective at detecting potentially cancerous cervical cells in a painless procedure and is routinely used for screening women between 20 and 50 years of age; conventional tissue biopsies for prostate cancer, however, are associated with side effects such as bleeding and infection and are traumatic for the patient, so are not used as screens. In any case, screening is discouraged if there is no effective treatment available.

Diagnosis, on the other hand, is undertaken following development of clinical symptoms. In cancer, approaches include: physical examination; immunological and molecular tests on urine/blood samples; imaging (CT/MRI, among others); and tissue biopsy. The cancer may then be characterised further to determine its stage and grade, location, and molecular characteristics, which may inform treatment choice.

### Types of liquid biopsy

Liquid biopsy is a relatively new approach to *in vitro* diagnosis. Since the first non-invasive prenatal testing (NIPT) kits (analysis of fetal DNA in maternal bloodstream) were commercialised in 2007, the industry has rapidly expanded with multiple small companies materialising. There has been a pattern of consolidation recently, as the technology has been de-risked and the commercial opportunity better understood.

The greatest advantages of liquid biopsies over conventional diagnostics is that they are pain-free and provide highly specific and sensitive 'real-time' results. Their rapid expansion has been underpinned by advances in DNA sequencing technology. Because this report is focused on Chronix, we do not detail the breadth of liquid biopsy approaches (summarised in the following table), rather concentrating on cfDNA. Each approach differs in its biological and technological strengths and weaknesses; however, it should be noted that those based on cfDNA tend to have the simplest workflow, as isolation of DNA is straightforward and computational analysis is relatively easy to distribute or out-license.

| Liquid biopsy approaches | | | |
|---|---|---|---|
| **Material circulating in blood stream** | **Example marketed product (manufacturer)** | **Details** | **Pros and cons** |
| Circulating Tumour Cells (CTCs) | Parsortix system (Angle plc) | CTCs are metastatic cancer cells –an increased number suggests increased cancer aggressiveness. | CTCs are used for both monitoring (by quantifying changes in cell number) and gene expression analysis – providing additional diagnostic information.<br>Low concentrations in early disease limit sensitivity; isolation of cells complex. |
| Exosomes | ExoDx™ Lung (ALK) (Exosome Diagnostics) | Exosomes are membrane-bound vesicles released from cells containing parent cell material (protein, RNA, etc.). | Molecular characterisation of exosomes allows detailed analysis of cancer cell function, as with CTCs. Isolation technology is complex. |
| cfDNA | Guardant360 (Guardant Health) | cfDNA is characterised based on a gene panel. | Simpler technology, clinically relevant result (e.g. therapy choice). |
| | CNI MONITOR (Chronix Biomedical) | cfDNA is characterised for copy number. | Simple, elegant solution, clinically relevant result with high accuracy. |

*Source: Hardman & Co Life Sciences Research*

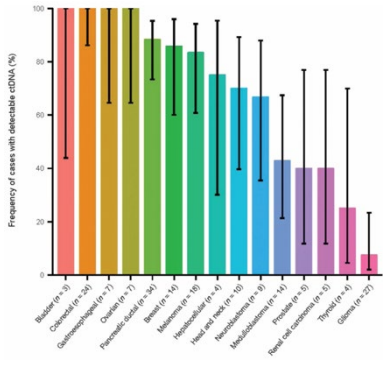
## DNA-based approaches

Most of the DNA-based liquid biopsies under development can be categorised according to the way that variation within circulating tumour DNA (ctDNA) is analysed. Certain characteristics of tumour cell DNA, whether sequence or structural variation, are statistically associated with specific cancers, and genome sequencing projects with millions of samples continue to discover more. Many liquid biopsies seek to identify these variants in order to predict the risk of disease, or for precision medicine i.e. to inform the use of therapies that are licensed for those particular variants. Most approaches fall under one of the headings below.

### *Complications*

There are some complications common to diagnostic approaches based on cfDNA. The most obvious is that some cancers will release more cfDNA than others, depending on their proximity to blood vessels. Then, sequence variation associated with cancer can be present also in a patient's healthy cells, and a cancer cell population is usually heterogeneous (i.e. some cells may have the cancer-associated variant and some do not). Furthermore, as resistance to treatment evolves, the prevalence of such variants within a patient's cancer may change. Finally, although some cancer therapies are licensed for targeted use against particular variants (e.g. vemurafenib (Zekboraf, Roche) for melanomas expressing mutated *BRAF*), these are still limited in number. For instance, studies show that less than 13% of patients receive mutation targeted treatments following genetic analysis[2].

**Presence of ctDNA varies by cancer type**




*Source: Bettegowda et al (2014[1])*

### *Single nucleotide polymorphism (SNP) profiling*

SNPs are naturally occurring single nucleotide changes in DNA sequence. Most SNPs represent background variation in the human genome, arise frequently, and have no effect whatsoever on the biology of the cell. However, some SNPs are representative of a population of cells and do result in altered proteins; some of these have been statistically linked to cancer. The commonly cited BRCA1 and BRCA2 breast cancer risk-associated gene variants are due to SNPs, and their presence indicates an increased risk of disease. Most SNP-based liquid biopsies in development are for targeted therapy selection in precision medicine, rather than for monitoring success of therapies as the prevalence of a SNP in ctDNA changes in serial samples. Finally, although many SNPs are associated with cancers, this does not imply causality, and this can undermine the clinical validity of some SNP-based approaches.

[1] Bettegowda et al. (2014) *Sci Transl Med* 19;6
[2] Tannock I.F. and Hickman J.A. (2016). Limits to Personalised Cancer Medicine. *NEJM* 375;13

### *Gene panels*

Similar to the SNP-based approach, gene panels look for known cancer-associated gene variants, or alleles, in a patient's ctDNA. One advantage of this approach is that it can be practical for treatment decision making, as the selected genes may be those with licensed therapies, so a single test returns a list of treatment options.

Also, some companies are developing panel-based blood tests for prognostic applications, e.g. the myRisk® Herediatary Cancer test (Myriad Genetics) for predicting the risk of eight cancers. Such tests interrogate hereditary germline alteration, e.g. from leukocytes, so they should not be confused with liquid biopsy tests.

### *Copy number variation*

Variation in the amount of genetic material or in its structure is widespread in human cancer cells[3]. This can result from an unusual number of chromosomes (aneuploidy) or copy number variation arising from deletion and duplication of large sections of DNA. As with SNPs and gene variants, some individual copy number variants (CNVs) are biomarkers of cancer, especially those that affect regulation of gene expression. The presence of cancer is often indicated on this basis, and Guardant's Guardant360 assay detects some CNVs in addition to sequence variants. Tests based on known CNVs require particularly high-quality DNA from the blood sample to permit the production of genome sequence that is as complete and contiguous as possible.

## Evaluating liquid biopsies

### *Considerations*

The main considerations when evaluating cancer diagnostics are their analytical validity, their clinical validity, and their clinical utility. Proper clinical studies must be carried out that confirm that the test works in patients and healthy controls. In the current environment, it appears that analytical validity (technical test performance) is well covered by requirements of regulatory bodies such as Clinical Laboratory Improvement Amendments (CLIA; see regulation page 19) in the US and the In Vitro Diagnostics Devices Directive (IVD; 98/79/EC) together with ISO/EN 15189:2014 in EU. Clinical validity is generally harder to confirm due to the complexity of disease biology and the size of the trials needed to confirm or reject associations among cancers and their genetic basis.

### *Performance in clinical decision making*

**Evaluating the performance of diagnostics**

| | Performance measure | Description | Note |
|---|---|---|---|
| Analytical validity | Sensitivity | $Sensitivity = \frac{number\ true\ positives}{number\ true\ positives + number\ false\ negatives}$ | True positive rate |
| | Specificity | $Specificity = \frac{number\ true\ negatives}{number\ true\ negatives + number\ false\ positives}$ | True negative rate |
| | Positive predictive value | $PPV = \frac{number\ true\ positives}{positive\ test\ results}$ | Depends on prevalence of condition in sample |
| | Negative predictive value | $NPV = \frac{number\ true\ negatives}{negative\ test\ results}$ | |
| Clinical validity | | How well the test is able to identify and predict the disorder of interest. This is underpinned by how well the genetic variant, or other marker, is associated with presence/absence/risk of the disease. | |
| Clinical utility | | How well does the test aid clinical decision making – diagnosis, treatment, management, or prevention of a disease – and its ability to improve clinical outcomes. | |

*Source: Hardman & Co Life Sciences Research*

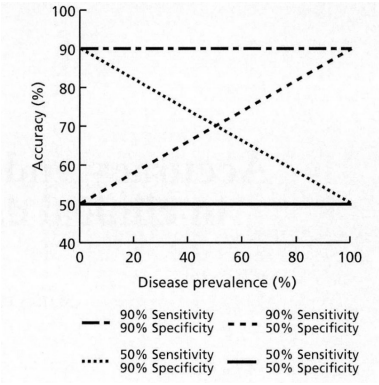
[3] Davioli T. *et al*. (2017). Tumour aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy. *Science* 355:261

**Diagnostic test performance**

a.

| | Disease present | Disease absent | |
|---|---|---|---|
| **Positive test result** | True positive (TP) | False positive (FP) | TP+FP |
| **Negative test result** | False negative (FN) | True negative (TN) | FN+TN |
| | TP+FN | FP+TN | Total |

b.




*Source: Eisenberg M. J. (1995)*

Studies evaluating the performance of liquid biopsies in patients are needed to demonstrate analytical validity and clinical utility to the regulators.

The value of a diagnostic is measured by its accuracy: the proportion of patients correctly identified as having or not having the disease in question[4]. This can be refined by its positive predictive value (PPV), for example, which describes the proportion of patients in the sample with a positive result who truly have the disease. This captures the reliability of the positive test result. However, because the prevalence of the disease in the sample is a factor of the PPV and NPV, these values should be assessed in a variety of different patient populations.

The sensitivity and specificity of a test depend less on the prevalence of the disease in question and can be thought of as characteristic of the test alone. They should be calculated using samples representative of the population of interest.

### *Limit of detection*

Methods that can detect a small number of tumour DNA fragments among an abundance of non-tumour DNA fragments (the 'noise') with high sensitivity and specificity are required. One of the greatest challenges in liquid biopsy is the limit of detection (LoD), and this is a particular challenge for methods that hunt for SNPs or other small sequence variants. The limit of detection is the lowest quantity of tumour DNA that is still detectable and analysable at a specified precision by the liquid biopsy test; therefore, the less prevalent the target variant is in a sample, the lower the limit of detection must be. Current liquid biopsies have a LoD between 0.1% and 5%, but these cannot necessarily be used as a point of comparison since they are dependent on the analyte being investigated and methodology. Clearly, tests intended for screening or early-stage cancer must have lower LoDs.

# Chronix's CNI approach – many advantages

## Elegant solution

Having a relatively simple premise, Chronix's CNI Monitor is an elegant and practical solution to some of the issues associated with the use of SNPs/CNVs/gene variants for monitoring the success of treatment or for early diagnosis of cancer.

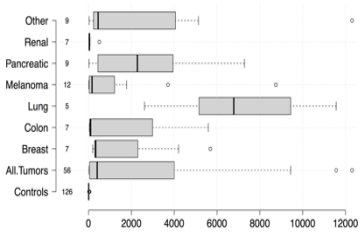
First, compiling genome-wide variation in copy number to a single score makes the CNI MONITOR less sensitive to mutational change that spans only a tiny portion of the genome. This avoids some of the issues associated with heterogeneity among cancer cells and with changes to the cancer genome that arise through evolution of resistance. Of course, once the genome is sequenced, Chronix's proprietary bioinformatic processing pipeline allows identification of particular loss and gain mutations in hotspots associated with specific cancers if necessary.

Secondly, it is versatile. Since copy number variation is associated with most types of cancer[3], a single test can be used to monitor tumour burden regardless of its type. If a patient's CNI score deviates significantly from normal, it indicates the presence of cancer. In addition, increased copy number variation has been shown to be associated with increased aggressiveness in cancers[3], and serial scores can therefore be used to monitor changes in cancer aggressiveness.

Thirdly, because higher or lower than normal copy number is characteristic of most cancers but is not characteristic of healthy cells, it is more discriminatory than tests based on SNP and single CNVs.

[4] Eisenberg M. J. (1995). Accuracy and predictive values in clinical decision making. *Cleveland Clinic Journal of Medicine* 62;5

## Baseline CNI score by cancer type




*Source: Chronix Biomedical*

## *Predicting the outcome of immunotherapy*

The performance of the TheraSure CNI MONITOR has been validated in multiple feasibility studies and in a completed, prospective clinical trial that showed that CNI score could predict the outcome of immunotherapy, at an early stage, with 91% sensitivity and 95% specificity.

### Design:

- prospective study;
- 56 patients with metastatic cancer refractory to chemotherapy;
- more than six types of cancer among the recruited patients;
- elevated CNI scores detected in 51 patients at baseline (see chart on left);
- discovery cohort: 21 patients; validation cohort: 30 patients;
- CNI score before immunotherapy and then prior to each cycle of treatment (up to six);
- imaging-based RECIST to define the efficacy of therapy; and
- comparator: conventional humoral markers.

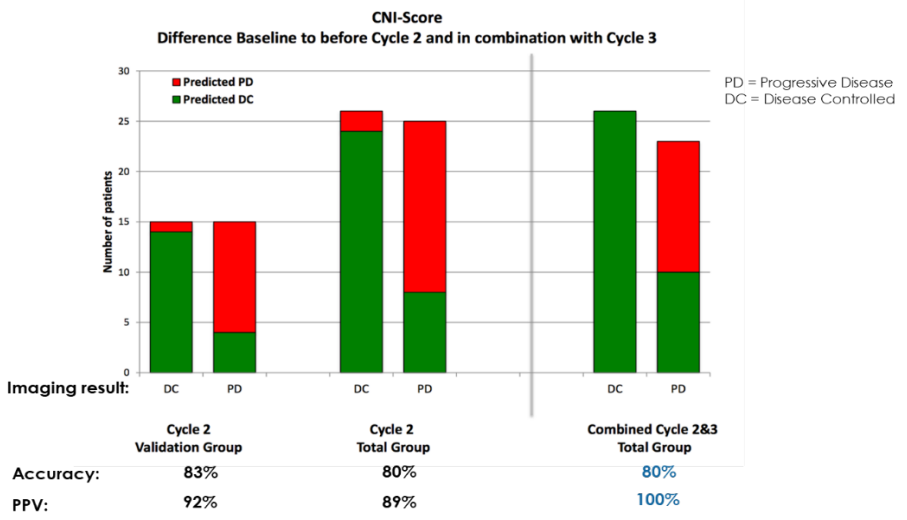
### Results:

- prediction of therapy outcome was possible as early as the second cycle;
- 91% (CI: 80-97%) sensitivity at 95% specificity; and
- accuracy: 86%

### Conclusion:

- early prediction of treatment failure of immunotherapy across a wide variety of cancer types.

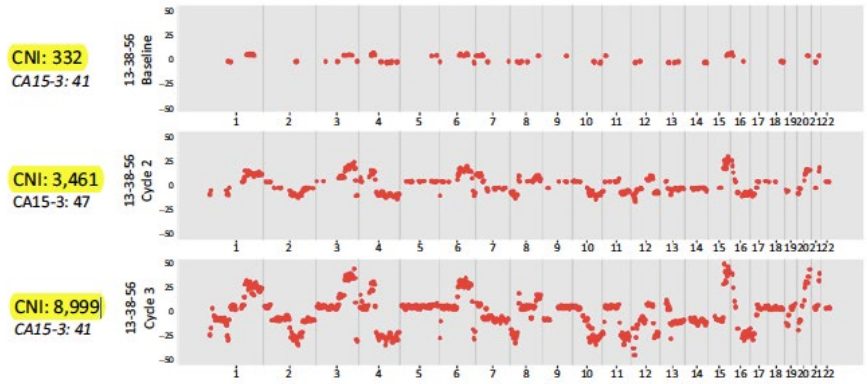
## Performance of CNI MONITOR in predicting therapy outcome




*Source: Weiss GJ et al. Clin Cancer Res. (2017); 23(17):5074-81*

An additional and important finding was that hyper-progression and pseudo-tumour progression could be predicted 6 to 9 weeks earlier using the CNI MONITOR than with routine imaging. The following graphic shows the increased tumour burden in a breast cancer patient as the cycles of immunotherapy progressed. The CNI score deviates further from zero, a diagnosis that was not evident using the biomarker CA15-3.

## CNI in breast cancer progression under immunotherapy




*Source: Weiss GJ et al. Clin Cancer Res. (2017); 23(17):5074-81*

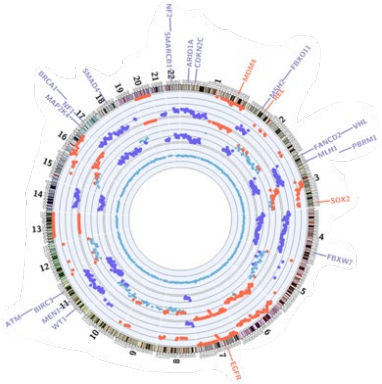
When the results from this trial are combined with the feasibility studies, the accuracy of CNI MONITOR is demonstrably higher than that of competing technologies.

## TheraSure CNI MONITOR more accurate

| Approach | Accuracy |
|---|---|
| CNI MONITOR | 86-92% |
| Gene panels | 70%-80% |
| CTC approaches | 70%-80% in late stage cancer |
| SNP approaches | Variable |
| Conventional protein/immunological diagnostics | <70% |

*Source: Chronix Biomedical*

## Reads aligned to human genome

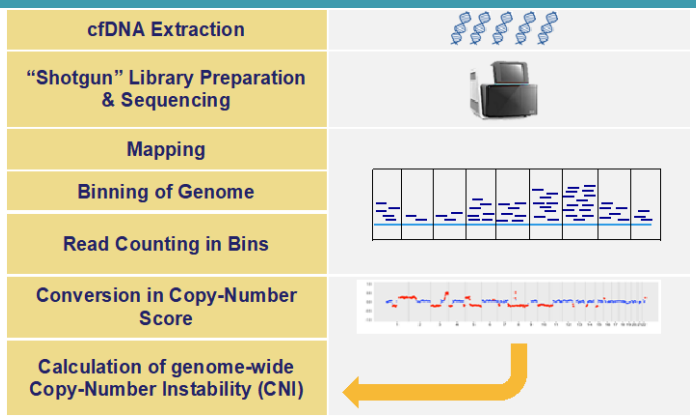


*Source: Chronix Biomedical*

# Generating CNI scores

Chronix's proprietary bioinformatic processing pipeline allows identification of loss and gain mutations in hotspots associated with specific cancers as outlined in the graphic below. A shotgun approach is used for the DNA library, which means that the DNA is broken into random fragments for sequencing. Combined with the 'mapping' stage, which involves aligning the sequence reads directly against a reference genome from Chronix's proprietary genome database, this means that no prior knowledge of the DNA target is required – i.e. it is a '*de novo*' approach. As a result, the test is applicable to all patients and cancers. Quality control steps, to account for sequencing errors or errors in mapping, are also included.

## CNI MONITOR bioinformatic pipeline




*An Illumina NGS platform is used for sequencing*
*Source: Chronix Biomedical*

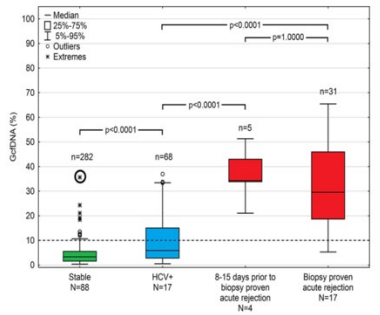
# TheraSure Transplant MONITOR

The TheraSure Transplant MONITOR test has also been validated in several clinical studies, involving an approximate total of 600 kidney, heart, and liver transplant patients and more than 5,000 blood samples. Studies show the test to have a very strong ability to reliably demonstrate that there is no rejection – i.e. it has high negative predictive values (PV) – thereby avoiding unnecessary biopsies in ca.30% of potential rejection cases. This improves patient outcomes and also reduces unnecessary costs.

| TheraSure Transplant MONITOR | | | | |
|---|---|---|---|---|
| Organ | Sensitivity | Specificity | Negative PV | Positive PV |
| Liver | 90% | 93% | 99% | 58% |
| Heart | 76% | 91% | 95% | 49% |
| Kidney | 79% | 80% | 97% | 28% |

*Source: Chronix Biomedical*

Elevated GcfDNA in liver transplant rejection (red boxes)




*Source: Chronix Biomedical*

## *Testing process*

Broadly speaking, the Transplant MONITOR quantifies graft-derived cfDNA in the patient's bloodstream using digital droplet PCR targeting a set of predefined genetic loci that are informative about the patient based on their ability to discriminate the transplant genome from the patient's genome. For new patients, this testing set must be identified once, prior to monitoring (again, from a blood sample), and is a quick and simple process.

## *Advantages*

Most important, is that the test can be turned around within a day. Transplant rejection and patient decline can happen fast (acute rejection) and a timely therapy is crucial. It is the **only test** on the market that can be used for all three major transplantations: kidney, liver and heart.

# Competition

## Cancer

As mentioned earlier, there are a number of different technologies trying to address the cancer diagnostics and monitoring markets. In the same way that Chronix is uniquely positioned with its CNI score in the *in vitro* molecular diagnostics market, other companies are uniquely positioned with their technologies (e.g. Oncimmune with its autoantibody technology). In contrast, there are very many players operating in the SNP and gene-panel diagnosis and precision medicine space, as described in the following table.

The large equipment and service providers, such as Illumina, LabCorp, Roche and Quest, have not been included in the table as their activities in liquid biopsies and/or specialist tests are very small within their groups' diverse operations. Where these companies come into play is in M&A. Smaller companies are allowed to take all the risk in developing novel tests but are approached once the technology is substantially de-risked and there is evidence of commercial success. These large players have the financial muscle and operational resources to commercialise the test worldwide.

| Closest liquid biopsy competitors to Chronix | | | | | |
|---|---|---|---|---|---|
| **Autoantibody** | **Genome-wide copy number variation** | **CTC** | **Protein biomarker** | **Genome-wide sequence variation** | **SNPs, Gene panels, Epigenetics** |
| Not molecular diagnostic | | | Conventional approach | Ultra-deep sequencing | |
| Oncimmune | Chronix Biomedical | Adaptive Biotech*<br>Agena Biosciences*<br>Angle<br>Biocept<br>Cynvenio*<br>EKF Diagnostics<br>Epic Sciences* | OPKO Health | Grail* | Exosome Diagnostics*<br>Foundation Medicine (Roche)<br>Guardant Health<br>Inivata*<br>Oxford Biodynamics<br>Personal Genome<br>Sysmex Inostics |

*CTC = Circulating tumour cells; SNPs = Single nucleotide polymorphisms*
** private company*
*This table is not comprehensive*
*Source: Hardman & Co Life Sciences Research*

## Transplant

Within the field of transplant monitoring, the main competition to Chronix comes from CareDx, which markets a donor-derived cfDNA test, AlloSure, for kidney transplant patients in the US only. AlloSure was launched in October 2017 with the aim to improve management of long-term post-transplant care by reducing the number of invasive biopsies and by ascertaining the appropriate dose of immunosuppressants.

The goal of CareDx and Chronix is to provide a better surveillance solution for transplant patients through:

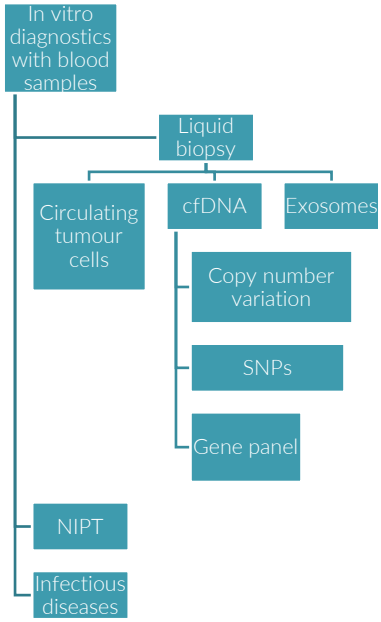
- Generation of highly accurate and quantitative results that differentiate rejection from non-rejection status;
- using a non-invasive procedure that does not create risks to the recipient;
- can be easily implemented; and
- can detect organ rejection much earlier than with standard approaches.

The liquid biopsy approach satisfies all these goals through its ability to provide results with a timescale and a frequency that allows informed and effective treatment decisions, without harm to the patient. In this field, the advantages offered by Chronix are that:

- It is the only company with IP protection in the EU; and
- its technology is the only one applicable to all major solid organ types, and is, therefore, the only universal rejection monitoring assay.

# Commercial strategy

**Molecular *in vitro* diagnostics**




*NIPT: Non-invasive prenatal testing*
*Source: Hardman & Co Life Sciences Research*

Chronix is well on its way to commercialisation, with its TheraSure CNI and Transplant MONITOR tests already launched through its distribution partner, Amedes, in Germany. Although the molecular *in vitro* diagnostics market is crowded as a whole, the liquid biopsy segment is a high growth prospect, and Chronix is extremely well placed within it to gain substantial market share for the following reasons:

- **First-mover advantage:** few copy number variation-based cfDNA diagnostics and scientifically sound TheraSure technology provides a real first-mover advantage.
- **Strong intellectual property:** broad patent protection, clear IP strategy, strong know-how underpinned by a specialist management team.
- **Clear market access strategy:** company business strategy takes in to account the complex and changing regulatory and reimbursement environment for LDTs; tests have strong health economic case.

## First-mover advantage in cancer

Chronix's primary competitive advantage is the fact that it is unique in having marketed technology based on genome-wide copy number variation. Several companies, including Guardant Health, are marketing liquid biopsies that include analysis of targeted CNVs; however, to our knowledge there are no other marketed technologies equivalent to the CNI score. Because there is not a clear regulatory approval pathway for LDTs currently in place, being the first to market an approach provides a real advantage over the multitude of new technologies.

## Broad patent protection

**Chronix Biomedical granted and allowed patents**

| Title | Country | Status | Priority date | Issue/Allowance date | Patent number | Inventors |
|---|---|---|---|---|---|---|
| Diagnostic detection of nucleic acids | US | Granted | 4 October 1996 | 5 February 2002 | US6,344,317 | H.U. |
| Detection of nucleic acids to assess risk for bovine spongiform encephalopathy | US | Granted | 9 September 2004 | 6 May 2008 | US7,368,243 | E.S., L.L., H.U. |
| Prostate cancer associated circulating nucleic acid biomarkers | Europe | Granted | 4 June 2010 | 6 September 2017 | EP2,576,837 | E.S., J.B., H.U. |
| | Canada | Allowed | 1 June 2011 | 30 July 2018 | CA2801468 A1 | E.S., J.B., H.U. |
| | US | Allowed | 1 June 2011 | 2 October 2018 | US14,414,882 | E.S., J.B., H.U. |
| Breast cancer associated circulating nucleic acid biomarkers | Europe | Granted | 18 April 2011 | 14 August 2018 | US10,047,397 | E.S., J.B., H.U. |
| | Europe | Allowed | 18 April 2011 | 20 April 2018 | EP2558854 | E.S., J.B., H.U. |
| Personalised biomarkers for cancer | US | Granted | 14 December 2012 | 6 March 2018 | US9,909,186 | E.S., J.B., H.U. |
| | Europe | Allowed | 14 December 2012 | 7 May 2018 | EP2931922 | E.S., J.B., H.U. |
| Detection and quantification of donor cell-free DNA in the circulation of organ transplant recipients | Europe | Granted | 29 May 2013 | 31 Oct 2018 | EP3004388A2 | E.S., J.B. |

*US: United States Patent and Trademark Office; Europe: European patent office; Canada: Canadian Intellectual Property Office*
*H.U.= Dr. Howard Urnovitz; E.S.= Prof. Ekkehard Schütz; J.B.=Dr. Julia Beck*
*Source: Hardman & Co Life Sciences Research*

In the absence of a market barrier created by a comprehensive regulatory process, a strong patent position is essential for companies protecting against the launch of directly competing products. In particular, the sample preparation protocol and backend bioinformatic pipeline of LDTs can be patented. While it is outside the scope of this report to investigate the status of patents across the sector, it is clear that Chronix has a strong and broad patent portfolio that protects its key products. The portfolio is being updated continually as pipeline products pass through feasibility studies.

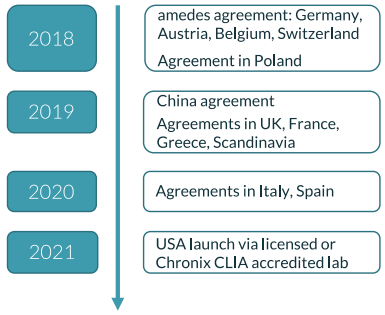
# Route to market

## Business strategy

Chronix made its debut launch this year with a distribution contract with Amedes in Germany. It has a very clear strategy for continuing its commercial momentum, which pivots on its short- to mid-term focus on the LDT monitoring product market (rather than screening or treatment selection). As exemplified by the Amedes deal (see below), the company's business model is straightforward and scalable, being based on out-licensing the technology to accredited laboratories, while conducting the bioinformatic processing in house. In return for this, Chronix will receive a service fee plus a royalty/licence fee per test.

Given the regulatory and reimbursement barriers to US entry, Chronix is focused on expansion within Europe. Discussions are underway also with potential partners in China.

**Launch plan**




*Source: Chronix Biomedical, Hardman & Co Life Sciences Research*

## European launch

### *Distribution partnership with Amedes*

Chronix signed its first commercial agreement on 27 June 2018, with Amedes, an established private German clinical laboratory group. It is owned by the French Private Equity Fund Antin, which bought it for approximately €800m in 2015. Amedes will market the tests through a subsidiary, called the Liquid Biopsy Center GmbH, incorporated in Gottingen, Germany.

Chronix has out-licensed its CNI and Transplant MONITOR tests to Amedes according to the following deal terms:

- Exclusive licence for covering Germany, Austria, Switzerland and Belgium in return for a substantial, but undisclosed, up-front payment.
- Chronix to receive a fixed fee plus a royalty/licensing fee for each test performed.
- The agreement is for 15 years and subject to a minimum number of tests being performed each year.
- The two companies will work together for the first 36 months of the contract on a market penetration strategy.
- Minimum annual sales targets for Amedes.

The partnership agreement includes a three-year market penetration strategy, which will be delivered through Amedes' existing infrastructure and sales team of approximately 70 people.

For the CNI MONITOR, blood samples are sent to Amedes' Medical Service Center in Hanover for DNA extraction and sequencing. This laboratory is accredited to ISO/EN 15189 standards. The digital sequence reads are subsequently downloaded

by Chronix for analysis and calculation of CNI score. Amedes already processes >150,000 laboratory samples daily and has the capacity and expertise to process Chronix's samples from Europe even at peak.

### *Agreement in Poland*

Chronix, in conjunction with Amedes, has also recently signed a licensing deal with a clinical testing laboratory in Poland to make the test available in that country. In the initial stages of this contract, blood samples will be sent to Amedes to generate the sequencing data and Chronix will again perform the computational analysis.

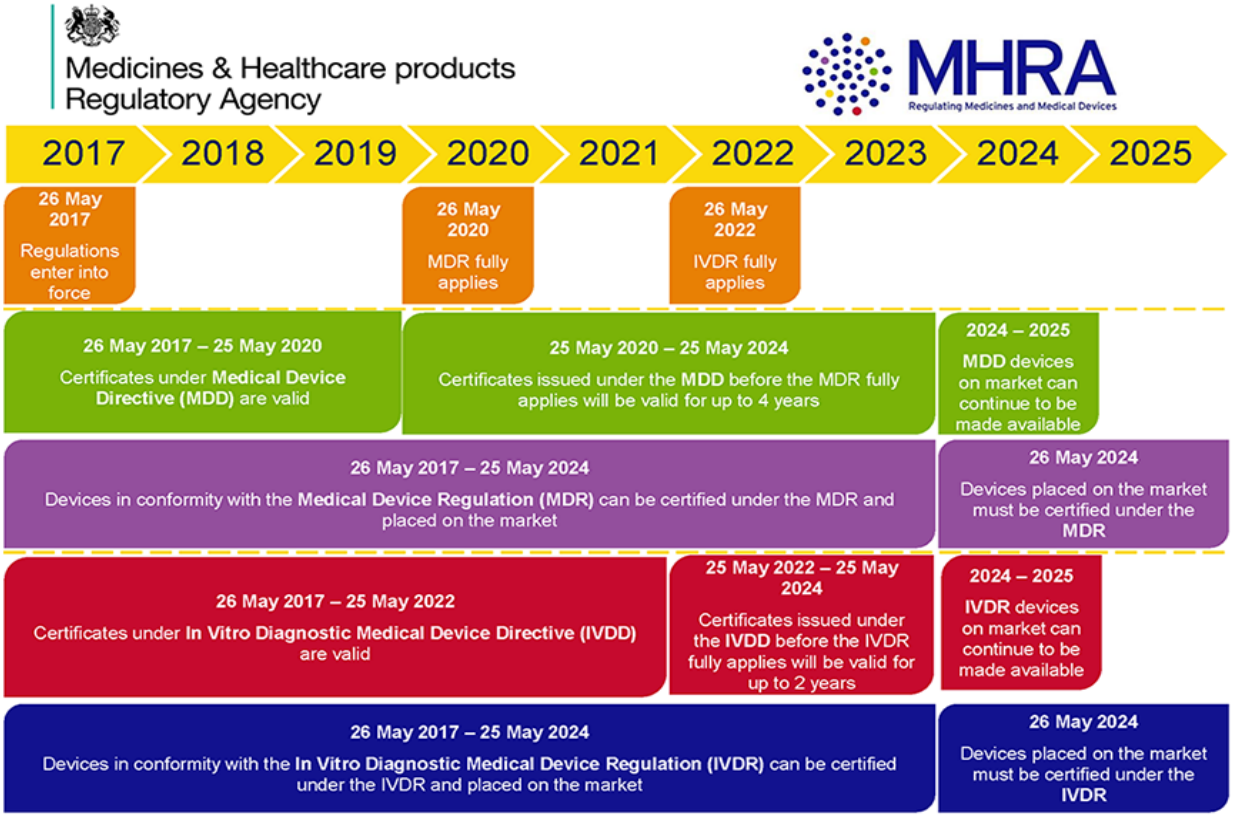
### *Additional geographical expansion*

Following its strong start in securing access to central Europe through its partnership with Amedes, Chronix is now looking to expand its presence more widely across Europe for launch in additional regions.

### *Regulatory and reimbursement strategy*

LDTs are not required to have CE marking under the current European In Vitro Diagnostics Devices Directive (98/79/EC) before being commercialised. However, a new In Vitro Diagnostic Regulation (IVDR) will come into force in 2022, with extensive changes to the regulatory changes for *in vitro* diagnostic devices (as Chronix tests are). Under IVDR, Chronix's tests will fall into the lowest risk class (Class D, a general IVD), which can obtain CE marking following self-certification.

**Timetable for the introduction of new EU medical device regulations**




*Source: Medicines & Healthcare products Regulatory Agency*

Chronix is taking the prudent and forward-looking view of ensuring that its TheraSure tests comply with the IVDR ahead of 2022. This will provide a competitive advantage as the tests will have CE marking as soon as possible once

the regulations come into effect. No notified body is required to provide CE marking for class D products; Chronix is already putting together the documentation for third-party audit. In the long term, once CE mark is achieved, Chronix intends to embed its proprietary CNI MONITOR algorithm into a software package for full distribution to third parties.

Laboratories performing the sampling and DNA sequencing should, however, be accredited to ISO standards – as mentioned, Amedes is fully accredited to carry out TheraSure testing in accordance with ISO 15189. It is notable that Amedes is the first laboratory in Germany to obtain this certification. In terms of EU regulation then, TheraSure when performed in Amedes' labs, is equivalent to CE marking standards.

In terms of reimbursement, in Europe it is on a country-by-country basis. Chronix has received reimbursement for the CNI MONITOR from major insurance companies in Germany, which lends a seal of approval for seeking reimbursement in additional countries. Regardless, the value proposition is one of reasonable pricing (afforded by low cost of goods), improved patient outcomes vs. conventional monitoring approaches, and reduced impact on payer budgets.

## US market entry

The regulatory and reimbursement environment in the US is complex and uncertain, providing significant hurdles to all manufacturers of LDTs. For this reason, Chronix will not seek entry to the US market immediately. It has the option to distribute its TheraSure products either as a partnership with CLIA-accredited laboratories, for which it is already in discussion with several potential licensees, or to set up its own CLIA-accredited laboratory (see regulatory considerations, below) for direct marketing.

It should be noted that there is an approved cfDNA transplant monitoring product in the US already, called AlloSure and marketed by CareDx, which has received reimbursement approval from Medicare. This is very encouraging validation of the technology; however, the price of AlloSure is likely to be in the region of $2,500 per test and as such is expensive. In addition, its price and quality are highly competitive and Chronix will likely out-license the test as an LDT to selected CLIA laboratories.

### *Regulatory considerations*

Regulation of LDTs and other medical devices falls under CLIA and FDA oversight, which differ in purpose but are complementary. CLIA is a programme regulated by the Centers for Medicare & Medicaid Service (CMS) that ensures quality laboratory testing, and therefore the analytical validity of genetic tests being carried out. It does not, however, cover the clinical validity or utility of the test/service itself. This is where complications arise for LDTs.

The FDA defines an LDT as an *in vitro* diagnostic test manufactured by and used within a single laboratory with a single CLIA certificate. LDTs, unlike *in vitro* diagnostic devices, are not currently required to be cleared or approved by the FDA before being sold. Resultingly, LDTs are sometimes used as a regulatory loophole, which has facilitated the marketing of many high-risk and unvalidated tests. The FDA has proposed legislative changes that would bring LDTs under FDA oversight, to ensure that clinical validity is established before marketing.

Since this is currently draft guidance only, Chronix is taking the pragmatic and cautious approach to the uncertainty in the market by beginning the studies needed to achieve FDA approval for its CNI MONITOR as a traditional Class III medical device. This requires going down the 510(k) route, whereby clearance is achieved by demonstrating equivalence to a legally marketed 'predicate device'.

Chronix has selected pancreatic cancer, where early identification of responders and non-responders to therapy provides particular benefits, as the indication for 510(k) regulatory approval in the first instance. The predicate device is the CA19-9 radioimmunoassay blood test that detects levels of antigen associated with pancreatic cancer cells, the widely accepted standard at present.

The pancreatic cancer trial is underway:

- **Primary-endpoint:** Comparison to CA 19-9 (predicate device)
- **Single-arm study:** 150 patients in Germany and the US
- **First line treatment:** Folfirinox or gemcitabine +/- Abraxane
- **CNI MONITOR:** Test pre-treatment and after cycles 1, 2 and 4
- **Preliminary data:** CNI MONITOR achieves ~90% predictive value for detecting progressive disease and ~95% predictive value for disease control.

### *Reimbursement considerations*

Reimbursement bodies often require information on clinical validity and utility for pricing decisions. In 2018, Medicare launched the 'Protecting Access to Medicare Act' (PAMA), which changes Medicare reimbursement in a move towards market-based pricing. This affects outpatient reimbursement, billed using CPT codes, adding further complexity to an already complicated system.

Given hurdles in the US, Chronix will concentrate on running studies in Europe in the first instance. Once sufficient evidence is collected, future achievement of FDA approval and reimbursement should be easier.

## Market access

In addition to prostate cancer, five cancers where early identification of responders is particularly beneficial to health outcomes and economics have been selected for separate trials. These will help with the engagement of KOLs, aiding market access in both Europe and the US. These are:

- Ovarian cancer
- Breast cancer
- Hepatocellular carcinoma
- Non-small cell lung cancer
- Colorectal cancer

# Commercial market

## Global market

Hardman & Co estimates that the *in vitro* molecular diagnostics (IVMD) market was worth about $10bn in 2017. This is composed of a number of distinct and diverse segments. One such segment is made up of smaller companies that offer proprietary tests from single laboratories (i.e. not machines/kits), which we estimate is currently worth $3.0-3.5bn. The majority of these are LDTs. Even this segment can be sub-divided, with the bulk of the sales targeting diagnostics for cancer (ca.62%) and NIPT (ca.25%). The activities of Chronix can be viewed alongside the global cancer IVMD market, which we estimate was worth ca.$2.05bn in 2017 and looks set to rise 23% to $2.52bn in 2018. This market is dominated by sales of tests in the US. The following table shows the breakdown of this market segment which has seen CAGR of 19% over the past three years.

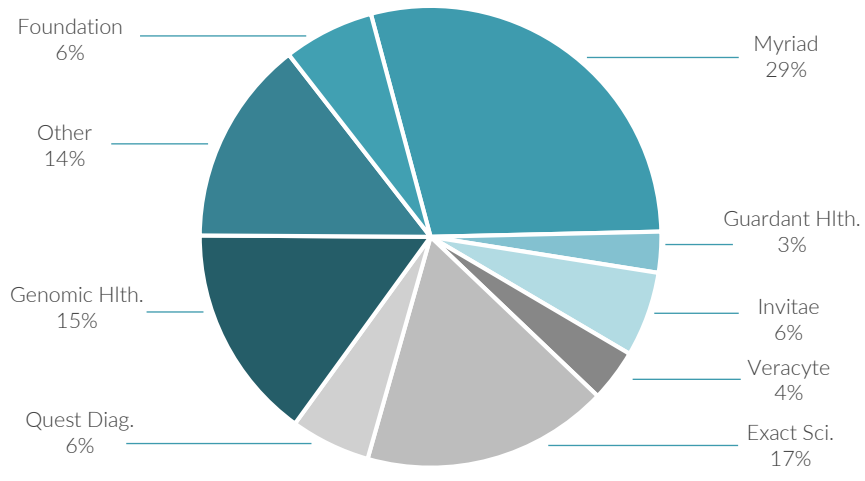
**Development of the oncology laboratory diagnostics market**

| Year to December ($m) | 2015 | 2016 | 2017 | 2018E | CAGR |
|---|---|---|---|---|---|
| Myriad Genetics | 706 | 687 | 730 | 725 | 1% |
| Exact Sciences | 39 | 99 | 266 | 435 | 123% |
| Genomic Health | 288 | 328 | 341 | 380 | 10% |
| Foundation Medicine | 72 | 60 | 92 | 160 | 31% |
| Invitae | 8 | 25 | 65 | 150 | 162% |
| Quest Diagnostics | 90 | 105 | 122 | 141 | 16% |
| Veracyte | 50 | 65 | 72 | 92 | 23% |
| Guardant Health | 14 | 24 | 42 | 72 | 71% |
| Other | 215 | 260 | 315 | 362 | 19% |
| **Oncology lab market** | **1,482** | **1,654** | **2,045** | **2,517** | **19%** |

*Source: Hardman & Co Life Sciences Research*

The following graphic translates the specific sales data provided in the table above into a pie chart showing the leading players in 2018. Given that most companies have reported nine-month financial results, we are confident about our forecasts. The strong position of Myriad Genetics is being eroded by the rapid growth rates being reported by the smaller companies with specific, more highly priced molecular tests.

**Oncology laboratory diagnostics market – 2018E**




*Source: Hardman & Co Life Sciences Research*

In terms of the IVMD transplant monitoring market, CareDx is a quoted US company under the ticker CDNA.OQ that is likely to generate sales of ca.$65m in 2018E. Its enterprise value is ca.$900m, giving it an EV/sales multiple of 13.8x in 2018.

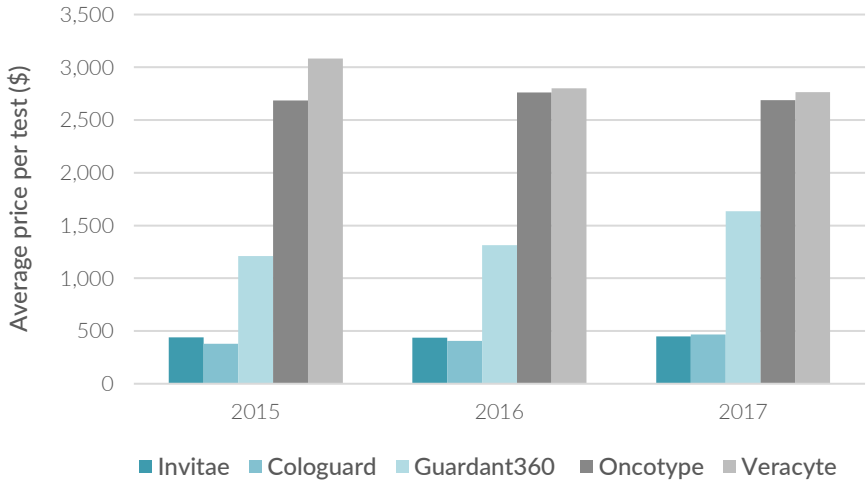
## Pricing of liquid biopsy tests

An analysis of pricing highlights significant differences among tests. Products seem to fall into two categories: those that are used frequently but offer less value-added information, which are priced below $500; and those that are very specific and allow clinical decisions to be made with respect to therapeutic activity. The following chart shows two of each.

By way of example, Genomic Health is using its Oncotype diagnostic genomic intelligence platform to address both the over-treatment and optimal treatment of early-stage cancer. It provides large amounts of clinical and genomic data which can be converted into clinically actionable results for the purposes of treatment planning. Supported by a range of large clinical trials. Genomic Health has been able to prove a strong pharmaco-economic benefit from using Oncotype DX that has enabled it to obtain an average test price in excess of $2,500, which is still a significant discount to its official list price in the range of $4,400-4,600 dependent on cancer type.

More recently, Guardant Health has entered the market with its Guardant360 precision oncology liquid biopsy test, in 2014. Since launch, the average price achieved per test has been steadily rising, reaching $2,292 in 1H'18 (data not shown), more consistent with the prices being achieved by Genomic Health and Veracyte.

**Price differential observed between different tests**




*Source: Hardman & Co Life Sciences Research*

## Potential market for Chronix

Although we do not know the price that is being charged by Amedes for the Chronix tests, given the health economic benefits of TheraSure CNI, it is likely to be priced to end-users at a figure commensurate with the prices being received by Genomic Health for Oncotype DX. It is normal practice for the laboratory/distributor to retain 50% of the gross margin, with the remainder being passed on to the originator/licensor. These assumptions would fit in well with the information that has been disclosed about the Amedes deal (see page 17).

## Cancer monitoring

We believe that the opportunity for Chronix is substantial because the majority of Chronix's competition are focused on developing molecular diagnostics for the early detection of cancer and for the US market. In contrast, Chronix is focused near-term on therapeutic monitoring in Europe. In the medium term, with CE marking, Chronix will be able to expand into other territories that recognise this rubber stamp, opening up further big opportunities. The company is also seeking to address the cancer monitoring markets in both the US and China.

## Transplant

The unmet need for rapid and early detection of organ rejection provides an excellent opportunity for Chronix. Due to the patient population, however, this market would be much smaller than the cancer market for liquid biopsies and tests are likely to command lower prices. On the other hand, the number of tests per patient life is a multiple compared with that of cancer patients.

## Cancer screening

The market for accurate and reliable screening tests for cancer is clearly potentially very large, and certainly larger than that of cancer monitoring. The current status of screening tests is that there is not a one size fits all and successful development of a cost effective and reliable test could generate very high revenues. Chronix has the IP to develop such a test, and this is on the mid-to-long term agenda. As mentioned, this would require very large patient trials, as evidenced by the >$1bn invested to date by Grail. The Chronix approach to developing a screening test is likely to be far simpler than Grail's, and the company believes it can be developed for $20-30m since the approach will only require the collection of 10,000 to 15,000 samples.

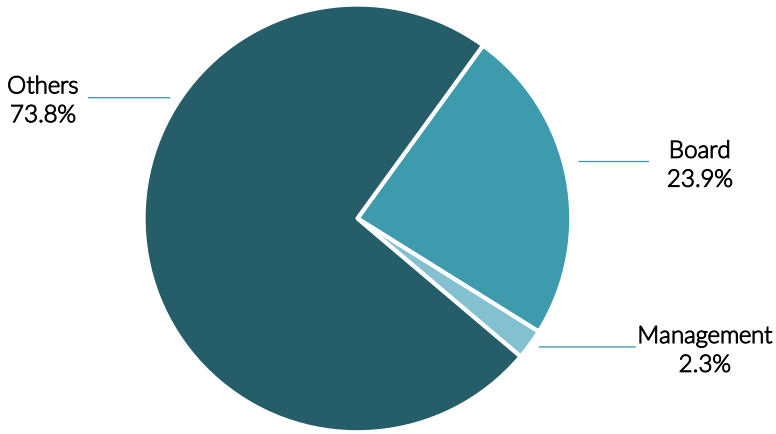
# Financials & valuation

## Funding history

Since incorporation, Chronix has raised a total of $44.6m through a series of funding rounds at an average price of $0.27 per share. The last round of funding began 15 months prior to the signing of the Amedes agreement. That round of funding provided the resources necessary to allow Chronix to negotiate a significant licence agreement. Subsequent to this funding, Chronix increased IP protection through the granting of a number of patents, and signed a significant long-term commercial agreement with Amedes, which has an NPV of at least $92m, based on a minimum annual number of tests. The solid IP-protection the company received in the last 18 months and the material licence contract were not reflected in the 2017-18 funding round, from which the pre-money valuation in this report is derived.

At the time of writing (31 October 2018), there were 164.7m common and preference shares in issue, 26.5% being held by the Board and management. On a fully diluted basis, taking into account the outstanding warrants and 20% option pool and anti-dilution rights, the company would have 279.6m shares is issue.

**Shareholders**




*Source: Chronix Biomedical*

## Financial forecasts

- **Sales:** Comprised of fee per test and licensing fee, largely from the Amedes contract over the forecast period.
- **COGS:** Minimal costs associated with computational analysis and preparation of test reports.
- **SG&A:** Corporate overhead plus the investment with Amedes to undertake the market penetration strategy over the next three years.
- **R&D:** Further investment in oncology therapeutic monitoring, and development of the test for monitoring transplant graft rejection. Little spend is associated with the development of a screening test for early cancer diagnosis.
- **Funding:** Forecasts assume that the company raises $20m in the next funding round to take it through to cashflow breakeven.

- **Cashflow:** R&D spend will be carefully controlled and possibly deferred to ensure that the funding gets Chronix close to cashflow breakeven. We recognise that development of a screening test would be very costly.
- **Balance sheet:** Cash in the balance sheet will be boosted by the funds raised in the ongoing funding round. Forecasts are based on a raise of $20m.

| Summary financials | | | | | | |
|---|---|---|---|---|---|---|
| Year-end Dec ($m) | 2015 | 2016 | 2017 | 2018E | 2019E | 2020E |
| Profit & Loss | | | | | | |
| Sales | 0.00 | 0.00 | 0.00 | 0.82 | 3.48 | 5.67 |
| COGS | 0.00 | 0.00 | 0.00 | -0.02 | -0.10 | -0.20 |
| SG&A | -1.91 | -2.27 | -2.03 | -2.34 | -3.51 | -4.21 |
| R&D | -1.90 | -2.26 | -1.33 | -1.50 | -6.00 | -5.00 |
| Other income | 0.00 | 0.00 | 0.00 | 0.25 | 0.00 | 0.00 |
| **Underlying EBIT** | **-3.81** | **-4.53** | **-3.36** | **-2.78** | **-6.13** | **-3.75** |
| Share-based costs | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Exceptional items | 0.00 | -0.20 | 0.00 | 0.00 | 0.00 | 0.00 |
| Net financials | -0.07 | -0.01 | -0.11 | -0.07 | 0.05 | 0.17 |
| Underlying pre-tax profit | -3.88 | -4.54 | -3.47 | -2.85 | -6.08 | -3.58 |
| Tax payable/credit | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **Underlying net income** | **-3.88** | **-4.54** | **-3.47** | **-2.85** | **-6.08** | **-3.58** |
| Average no. shares (m) | 92.5 | 218.1 | 105.0 | 152.2 | 207.5 | 221.8 |
| **Underlying basic EPS ($)** | **-0.04** | **-0.02** | **-0.03** | **-0.02** | **-0.03** | **-0.02** |
| U/l fully-diluted EPS ($) | -0.03 | -0.02 | -0.02 | -0.01 | -0.02 | -0.01 |
| | | | | | | |
| Balance sheet | | | | | | |
| Share capital | 35.15 | 38.07 | 40.61 | 44.51 | 64.51 | 64.51 |
| Reserves | -37.77 | -41.99 | -45.39 | -50.68 | -56.75 | -60.33 |
| Loans | 0.20 | 0.05 | 1.46 | 0.00 | 0.00 | 0.00 |
| *less:* Cash & deposits | 1.36 | 0.57 | 0.50 | 5.05 | 16.96 | 12.31 |
| **Invested capital** | **-3.77** | **-4.45** | **-3.81** | **-7.52** | **-7.09** | **-7.32** |
| | | | | | | |
| Cashflow | | | | | | |
| Underlying EBIT | -3.81 | -4.53 | -3.36 | -2.78 | -6.13 | -3.75 |
| Change in working capital | 0.21 | 0.26 | -0.10 | 0.04 | 0.06 | 0.07 |
| Operating cashflow | -3.44 | -3.50 | -3.70 | 0.70 | -7.99 | -4.45 |
| Capital expenditure | -0.01 | -0.05 | 0.00 | -0.05 | -0.10 | -0.20 |
| Capital increase | 4.11 | 2.92 | 2.21 | 3.90 | 20.00 | 0.00 |
| **Change in net cash/(debt)** | **0.66** | **-0.63** | **-1.49** | **4.55** | **11.91** | **-4.65** |
| | | | | | | |
| Opening net cash/(debt) | 0.50 | 1.16 | 0.53 | -0.97 | 5.05 | 16.96 |
| **Closing net cash/(debt)** | **1.16** | **0.53** | **-0.97** | **5.05** | **16.96** | **12.31** |

*Source: Hardman & Co Life Sciences Research*

# Valuation

Valuing private companies with relatively limited financial information and forecasts can be quite difficult; therefore, we use a multi-disciplinary approach to provide readers with as much information as possible in order for potential investors to make an informed judgement about whether Chronix is a good investment opportunity.

## DCF analysis

In our opinion, the best approach to valuing biotech companies is to prepare detailed discounted cashflow analyses of key products through to patent expiry and then to risk-adjust the NPV based upon industry standards for the probability of the product reaching the market. However, in order for this to be successful, there needs to be a long period of forecasts based on actual data derived from historic benchmarks. In this instance, the assets are only just entering the commercial phase and there is only a modest level of benchmark information available regarding liquid biopsies in order to limit the heavy influence of the terminal value to the DCF.

Nevertheless, in the case of Chronix, management appears to have signed a very good deal with Amedes. Even though the financial information about the deal has not been disclosed, management has indicated that the cashflows of the revenues based on annual minimum number of tests over the 15-year term of the contract generate an NPV of $92m using a WACC of 10%.

Using a few relatively straight-forward assumptions, this NPV has been tested, from which a matrix can be formed to provide readers with a view on whether the numbers are realistic/achievable:

- The price of the test to Chronix is estimated in the range $400-1,000 – the in-market price would be approximately double these figures.
- Minimum number of annual tests, when established, is estimated to be in the range 15-35,000.
- The licence access fee has been set at $25 per test.

It should be stressed that these are our assumptions, all of which might be incorrect. However, the data suggests that the NPV provided by management can be achieved if the test is priced (received by Chronix) at about $600-700, consistent with the actual cost of a liquid biopsy NIPT, and that the minimum number of tests per annum is 25,000-30,000. These are all based on an estimated licence fee per test of $25. The following table provides a matrix of NPV.

**Amedes contract – matrix of NPV to Chronix**

| NPV ($m) | | Price of test ($) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 400 | 500 | 600 | 700 | 800 | 1,000 |
| Annual minimum | 15,000 | 34 | 41 | 49 | 57 | 64 | 80 |
| | 20,000 | 43 | 52 | 62 | 72 | 82 | 101 |
| | 25,000 | 52 | 63 | 75 | 87 | 94 | 123 |
| | 30,000 | 60 | 74 | 88 | 102 | 116 | 144 |
| | 35,000 | 69 | 85 | 101 | 117 | 133 | 165 |

*Source: Hardman & Co Life Sciences Research*

## Comparative valuation

An alternative approach to valuation is to undertake a peer group comparison, whereby the value of Chronix can be put into context against the stock market valuations afforded to a group of similar companies. However, while this is a sound approach to take, in practise it is much less straightforward for a number of reasons:

- companies are all using slightly different technologies and approaches;
- even using the same approach, different targets/indications are being tackled;
- it is well known that the UK stock market affords lower valuations to companies compared with similar companies quoted on other stock markets.

Therefore, the peer group analysis has been divided into two tables – one consists of a group of AIM-listed UK peers working in the field of advanced specialist diagnostics; the second is a group of similar internationally quoted peers. It should be pointed out that a number of direct competitors in this area are privately owned and data is not available in order to derive an up-to-date valuation.

### *UK peer group analysis*

Peer group analysis suggests that there is scope for an upside potential

The companies detailed below are close peers of Chronix, all working in the field of specialist diagnostics/liquid biopsies, mostly in the field of oncology, but also at different stages in the commercialisation of their products.

- The average EV of UK peers is £76.3m (range £47.1m-£178.4m).
- The relative EV of UK peers to the latest funding round valuation of Chronix is in the range 1.5x to 5.8x, with a weighted average of 2.5x.

## UK peer group valuations

| Company | Angle | Chronix Biomedical | Inivata Ltd | Yourgene Health | EKF | Oncimmune | Oxford Biodynamics |
|---|---|---|---|---|---|---|---|
| Ticker | AGL | - | - | YGEN | EKF | ONC | OBD |
| Local currency | £ | $ | £ | £ | £ | £ | £ |
| Share price | 46.8 | 0.27 | 1.90 | 9.1 | 28.8 | 101.0 | 209.0 |
| Shares in issue (m) | 142.5 | 164.7 | 33.4 | 416.9 | 457.5 | 61.6 | 92.5 |
| Market cap. (£m) | 66.6 | 34.7 | 63.5 | 37.9 | 131.5 | 62.2 | 193.4 |
| Cash (£m) | 16.0 | 3.9 | 11.0 | 3.0 | 9.0 | 11.0 | 15.0 |
| Debt (£m) | 0.0 | 0.0 | 0.0 | -12.2 | -1.1 | 0.0 | 0.0 |
| **EV (£m)** | **50.6** | **30.8** | **52.5** | **47.1** | **123.6** | **51.2** | **178.4** |
| Relative EV (x) | 1.6 | - | 1.7 | 1.5 | 4.0 | 1.7 | 5.8 |

*Prices taken at close of business on 2 November 2018*
*Source: Hardman & Co Life Sciences Research*

### *Global peer group analysis*

Valuations afforded to the global peers quoted on international stock markets are generally higher and have a broad range. There are usually specific circumstances for this, such as differing technologies, different stages of commercialisation, a concentration on the US market, and different focuses of activity. Our group of peers has been limited to those that are more focused on actual molecular tests, as opposed to equipment manufacturers and/or service laboratories, and have an enterprise value of less than $2.5bn. Also, it should be reiterated that many of Chronix's immediate peers are privately owned companies for which only limited financial information is available regarding the valuation at the most recent funding round.

- The average EV of global peers is £765.9m (range £42.2m to £1,911.1m).
- The relative EV of global peers to the average funding round valuation of Chronix is in the range 1.4x to 62.1x, with an average of 25.0x.

## Global peer group valuations

| Company | Biocartis | Chronix Biomedical | Genomic Health | MDxHealth | Myriad Gen. | Neo-Genomics | OncoCyte | Natera |
|---|---|---|---|---|---|---|---|---|
| Ticker | BCART | - | GHDX | MDXH | MYGN | NEO | OCX | NTRA |
| Local currency | € | $ | $ | € | $ | $ | $ | $ |
| Share price | 12.48 | 0.27 | 72.6 | 1.86 | 38.4 | 18.0 | 2.0 | 22.3 |
| Shares in issue (m) | 51.1 | 164.7 | 35.9 | 59.9 | 70.9 | 81.6 | 40.7 | 60.9 |
| Market cap. (lc) | 637.8 | 44.5 | 2,603.1 | 111.5 | 2,723.3 | 1,465.4 | 80.9 | 1,359.1 |
| Market cap. (£m) | 562.5 | 34.7 | 2,030.4 | 98.3 | 2,124.2 | 1,143.0 | 63.1 | 1,060.1 |
| Cash (lc.m) | 91.3 | 5.0 | 152.9 | 32.7 | 211.3 | 9.5 | 11.0 | 88.8 |
| Debt (lc.m) | -38.2 | 0.0 | 0.0 | 0.0 | -9.3 | -138.5 | -2.0 | -123.3 |
| EV (lc) | 584.7 | 39.5 | 2,450.1 | 78.8 | 1,922.2 | 1,272.1 | 54.1 | 1,393.6 |
| **EV (£m)** | **515.7** | **30.8** | **1,911.1** | **69.5** | **1,499.3** | **992.2** | **42.2** | **1,087.0** |
| Relative EV (x) | 16.8 | - | 62.1 | 2.3 | 48.7 | 32.2 | 1.4 | 35.3 |

*Note: this peer group should not be considered comprehensive*
*Prices taken at close of business on 2 November 2018*
*lc = local currency*
*Source: Hardman & Co Life Sciences Research*

Both the UK and global peer analysis suggests that Chronix has considerable upside potential in its valuation, especially given that it has invested $45m to get the company where it is today, with a substantial commercialisation deal in place with an established and reputable clinical laboratory group.

## M&A activity

As highlighted earlier in this report, there is a plethora of small companies developing molecular diagnostic products based on liquid biopsies. The large global players in the field of diagnostics and clinical laboratory testing are quite content to let the small companies take all the development risk and then to acquire the company/technology when it has been de-risked and started commercialisation. The prices paid have represented a handsome return for investors. The following table highlights a few recent deals. The average price paid by acquirors has equated to an EV/sales ratio of 19.2x.

**Sector M&A activity**

| Date | Target | Acquiror | Consideration ($m) | Cash/(debt) ($m) | EV ($m) | Sales ($m | EV/sales |
|---|---|---|---|---|---|---|---|
| Jul-18 | Foundation Medicine | Roche | 5,102 | -54 | 5,156 | 210 | 24.6x |
| Jul-16 | Sequenom | LabCorp | 302 | -69 | 371 | 120 | 3.1x |
| Apr-15 | CAPP Medical | Roche | 96 | - | 96 | | - |
| Apr-15 | Foundation Medicine | Roche* | 1,630 | 232 | 1,398 | 60 | 23.3x |
| Dec-14 | Ariosa | Roche | 625 | 10 | 615 | 53 | 11.6x |
| Feb-13 | Verinata | Illumina | 450 | 3 | 447 | 12 | 37.3x |

**Roche initially acquired a controlling 61% stake*
*Source: Hardman & Co Life Sciences Research*

# Investment opportunity

Chronix is looking to raise $10-30m (our forecasts are based on a $20m gross raise) in a pre-IPO funding round to take the company through the early stages of commercialisation with Amedes, to finish/undertake supportive clinical trials to enhance its regulatory programmes, and to maintain/strengthen its patent position.

## Use of proceeds

The company's upcoming activities will be dictated by the quantum of funds raised in the next round. $5m is required to finish existing trials and support the initial commercial programme; a further $15m will be used to expand the trial programme and support the commercial rollout into more territories. Any move towards cancer screening tests would require considerably greater funding.

**Chronix trial and commercial programme**

| Use of first $5m funding | | Use of next $15m |
|---|---|---|
| Therapy monitoring | | Therapy monitoring |
| Pancreatic cancer | 2H'19 | Lung |
| Breast cancer adjuvant | 1H'19 | Colorectal |
| Ovarian cancer | 12 months | Melanoma |
| Multi-centre UK trials | | Recurrence in colorectal |
| Second opinion prostate cancer | 18 months | Recurrence in breast |
| Second opinion breast cancer | 18 months | |
| Commercialisation/working capital | | Commercialisation IP, and working capital |

*Source: Hardman & Co Life Sciences Research*

# Company matters

## Registration

Chronix Biomedical Inc. is a Delaware corporation with its registered office at:

5941 Optical Court
Suite 201
San Jose, CA 95138
United States

+1 408-960-2307
www.chronixbiomedical.com

## Board of Directors

| Board of Directors | |
|---|---|
| **Position** | **Name** |
| Non-executive Chairman | David Mackenzie |
| Non-executive director | William Boeger |
| Non-executive director | Paul Freiman |
| Non-executive director | Ralf Glaubitz |
| Non-executive director | Michael Jerstad |
| Non-executive director | Robert Leppo |
| Non-executive director | William Mitchell |

*Source: Company reports*

### *David Mackenzie – Chairman*

Mr. Mackenzie has 33 years of business experience, starting at age 17 when, along with five younger siblings, he created Jethro Development Ltd, an oil and gas exploration and production company that became profitable in its second year of operations, and provided the funds used to acquire major positions in subsequent business ventures. As President of the Lincoln Group of Companies, Mr. Mackenzie has 15 years of venture capital experience. Investments have resulted in the successful start-ups of Computer Motion (ISRG on NASDAQ), WestJet Airlines (WJA on Toronto exchange), Arxx Building Products, SideStep, Vovida Networks (acquired by Cisco for $100m in 2000), Telverse Comms. (sold to by Level 3 Comms. for $30m in 2003), Teamplate Inc. (acquired by Captaris Inc. for $11.5m in 2003), Sonic Mobility (acquired by Avocent Corp for $8m in 2004), ICEsoft Inc., Blizzard Energy (sold assets to Shiningbank Energy Income Fund for $275m in 2005), and Zenas Energy Corp. (ZNS on Toronto exchange). He also has 14 years experience in international commerce. Successful investments include: Maloney Industries (selling oil and gas equipment into many countries), Vlinx (China), and Osidle Baltyk (Poland). Mr. Mackenzie received a BA in Economics from Whitman College, Washington, and a BSc in Petroleum Engineering from Colorado School of Mines, Denver.

### *William Boeger – Non-Executive Director*

Mr. Boeger co-founded Chronix with Howard Urnovitz in 1997. He has 30 years' experience in venture capital investing in, and senior management of, both public and private early-stage companies. Previously, Mr. Boeger was Chairman and CEO of Calypte Biomedical. In his role as a venture capitalist, he has held senior positions at Quest Ventures and Continental Capital Ventures. Earlier in his career, Mr. Boeger worked as a Research Assistant at Harvard Medical School and also served on the faculty of the Tuck School at Dartmouth College. He received a BSc. from Williams College and an MBA from Harvard Business School. Mr. Boeger has worked actively with start-up companies and served on the Boards of Directors of numerous portfolio companies that have successfully completed an IPO or have been acquired by public companies.

### *Paul Freiman – Non-Executive Director*

Mr. Freiman's career spans 54 years in healthcare, starting as a salesman at ER Squibb & Sons in 1958, before joining Syntex as a salesman in 1962 and rising through the ranks. By the time of its acquisition by Roche in 1993, Mr Freiman had become its CEO and Chairman. From 1994-96, he founded and owned Third Age Consulting, San Francisco, consulting on Pharmaceuticals and Boards of Directors. From 1996-2009, Mr. Freiman was CEO of Neurobiological Technologies Inc, a California-based biotech company. More recently (2009-14), he has been a partner in Burrill Brasil Investimentos, Rio de Janeiro, helping to discover and fund a nascent Brazilian biotech industry as well as the delivery of healthcare in Brazil. He has served on the boards of numerous biotechnology and pharmaceutical companies, including the US-arm of Otsuka and currently serves on the board of NovaBay.

### *Ralf Glaubitz – Non-Executive Director*

Dr Glaubitz has more than 30 years' experience in biochemistry and diagnostics, initially studying biochemistry at the Free University Berlin, before moving to the Medical University Hannover where he was awarded a PhD. His whole working life has been dedicated to disease diagnosis in clinical laboratories in many cases either attached to or partnered with major hospitals in Germany. Latterly, Dr. Glaubitz has worked at clinical laboratories owned by the Amedes group in Hamburg, Kiel, and Hannover covering, among others, fertility, pathology and human genetics.

### *Michael Jerstad – Non-Executive Director*

Mr. Jerstad is a Partner at PrairieGold Venture Partners where he oversees all aspects of the firm's investment activities, from sourcing, structuring and negotiating investments to serving as a board member for portfolio companies. He currently serves on the boards of Grand Prairie Foods, Chronix Biomedical, PetMedicus Labs and Orasi Medical. Prior to joining PrairieGold, Mr. Jerstad worked in Piper Jaffray's Healthcare Investment Banking Group, specializing in M&A advisory services and public and private equity financing. Before that, he was an Attorney at Briggs and Morgan LLP, specialising in business litigation, employment law and contracts. He received a BA from Tufts University, a JD from Georgetown University, and an MBA from the University of Chicago.

### *Robert Leppo – Non-Executive Director*

Mr. Leppo has more than 30 years of investing experience, beginning as a Securities Analyst at Capital Research Company (1969-77). Since 1977, he has been self-employed as a private investor. Mr. Leppo has successfully developed ongoing strategies for investing in three markets: personal venture capital, US common stocks, and commodity futures. Increasingly in the past 20 years, he has focused on venture capital into start-up/early-stage companies and, since 1995, focused increasingly on internet-based companies. Major successful investments and board membership dates include: Information America (1983-92), Advent Software (1983-95), Best Internet (1995-97), MedSeek (1995-2000), ValueClick (1998-2000), OnPrem (1999-2000) and AirTreks (1998-2000). Significant major public stock positions were Coachmen Industries (1975-76), Nucor, Progressive Insurance, and most importantly, Circuit City. Mr. Leppo received a BA in History from Stanford University and an MBA from Harvard Business School.

### *William Mitchell – Non-Executive Director*

Dr. Mitchell is a Professor of Pathology at Vanderbilt University School of Medicine. He was awarded an MD from Vanderbilt and a PhD from Johns Hopkins University, where he served as an Intern in Internal Medicine, followed by a Fellowship at its School of Medicine. Dr. Mitchell has published more than 200 papers, reviews and abstracts dealing with viruses, anti-viral drugs and immune responses to HIV infection. Dr. Mitchell has worked for and with many professional societies, including the International Society for Anti-viral Research, the American Society of

Biochemistry and Molecular Biology, the American Society of Microbiology and government review committees, among them the National Institutes of Health, AIDS and Related Research Review Group.

## Executive team

### *Prof. Ekkehard Schütz – Chief Executive Officer/Chief Medical Officer*

Ekkehard has more than 25 years' experience in the research and development of medical diagnostics, with over 150 peer-reviewed publications, including reviews and book chapters. He joined Chronix in 2001 after working for over a decade in the medical laboratory at the University Hospital in Göttingen, Germany. Prof. Schütz is a leading authority on using computer-assisted analysis to develop cutting-edge molecular diagnostic services, and has received several awards in Molecular Diagnostics and Clinical Chemistry. He is the architect of the Chronix Biomedical cancer and transplantation tests using cell-free DNA, while also heading up a ISO/IEC 17025:2005 accredited laboratory. This combination of understanding computer science and molecular biology, together with being a physician running a clinical laboratory, has allowed him to develop critically needed diagnostics. He holds numerous patents and has a lot of experience in negotiating licensing agreements.

### *John DiPietro – Chief Financial Officer*

With more than 28 years of experience in financial management, public accounting and senior management of public and private companies, Mr. DiPietro joined Chronix as CFO in 2002. Previously, he has successfully completed three IPOs and has raised more than $200m of public/private debt and equity. He served as CFO and COO of Calypte Biomedical, Inc. from 1995-99. Previously, Mr. DiPietro served as CFO of Meris Labs, Inc., a clinical laboratory company, and Tripath Technology, Inc., a semiconductor company. He was a member of the Board of Directors of Calypte and served as Chairman of the Compliance Committee and as a member of the Audit Committee. Mr. DiPietro received a BSc from Lehigh University and an MBA from the University of Chicago Graduate School of Business. He is a Certified Public Accountant.

### *Howard Urnovitz, PhD – Chief Science & Strategy Officer*

Chronix Biomedical was founded by Dr Urnovitz in 1997. He continues to serve as Chief Science and Strategy Officer. He has been active in corporate biotechnology discovery and research for the past 30 years. Previously, Dr Urnovitz founded Calypte Biomedical, Inc., a manufacturer of HIV diagnostics, and served as CSO from 1988-2000. Prior to Calypte Biomedical, he served as Senior Scientist at the Institute of Cancer Research, Medical Research Institute, in San Francisco, California. Previous positions include Director of Molecular and Cellular Engineering at XOMA Corporation, and Director of the Hybridoma Facility, Laboratory of Experimental Pathology at the University of Iowa. Dr Urnovitz has published in scientific journals and has been an invited speaker or panellist at international scientific conferences and U.S Congressional hearings. He holds several patents related to immunoassay diagnostics. Dr Urnovitz received a BSc and MSc in Microbiology and a PhD in Microbiology and Immunology from the University of Michigan.

### *Julia Beck, Ph.D – Vice President of Research*

Julia has 17 years' experience working in molecular diagnostics, with more than 70 peer-reviewed publications, including original papers, book chapters, and conference contributions. She joined Chronix in 2006 and, following promotions, was appointed VP of Research in 2018. Julia gained considerable experience in the genomic analysis of animals and human using all the common techniques of molecular biology and genomic data analysis while workin towards her MSc and PhD, both awarded by Göttingen University, in 2003 and 2007, respectively.

# Risks

**It goes without saying that investments in small, privately owned, early-stage companies carry a significant risk and investors must be aware of this fact.**

In our opinion, the following risks are particularly relevant.

## Patent robustness

As with all med-tech and diagnostic products, there is risk that the intellectual property is insufficiently covered by global patents. Indeed, the potential to launch TheraSure Transplant MONITOR is being held back currently by the lack of appropriate patent cover.

## Regulatory approval

Chronix is operating in a field potentially subject to tight and changing regulation. Although some of its products can be launched as LDTs without formal regulatory approval, having FDA (via 510(k) and EU (via CE marking) regulatory approval confers considerable advantages and a certain level of market protection. Such regulatory processes are time consuming and need to be supported, generally, by potentially expensive clinical trials.

## Competition

Although the technology approach being taken by Chronix is unique, other technologies can be used to obtain similar outcomes, all with the aim of improving clinical decisions. The competition section (page 14) highlights the large number of companies developing and/or commercialising diagnostic tests and this ignores the large specialist clinical laboratory groups that control much of the market.

## Commercialisation and pricing

While Chronix has a sound commercial strategy in Europe, with the important deal signed with Amedes, it remains at a much earlier stage regarding the US. Pricing of products has been helped by the fact that some competitor products have been priced and are being reimbursed by payers at levels which will provide an adequate return. Strong pharmaco-economic data is required in order to obtain these pricing structures. However, as more products enter the market, it is conceivable that prices might come under some pressure.

## Dilution risk

Forecasts suggest that the ongoing funding round will be sufficient to reach particular milestones and commercialisation of TheraSure CNI MONITOR and TheraSure Transplant MONITOR. Coupled with the commercial deal with Amedes, the company will not require further capital over the forecast period. However, if the company decides to develop and compete in the early cancer diagnosis market, Chronix might require further development capital. Shareholders will have pre-emption rights on further new issues of shares but could suffer significant dilution if they do not participate in further funding rounds.

## Share liquidity

An investment in the company might not be suitable for all recipients of this publication as this is an investment for which there is no recognised market. It might be difficult for investors to sell their investments or to obtain reliable information about its value or the extent of the risk to which it is exposed.

# Glossary

| | |
|---|---|
| cfDNA | Cell-free deoxyribonucleic acid |
| CLIA | Clinical laboratory improvement amendments |
| CNI | Copy number instability (score) |
| CNV | Copy number variants |
| CTC | Circulating tumour cell |
| ctDNA | Circulating tumour deoxyribonucleic acid |
| CT | Computed tomography scan |
| IVMD | *In vitro* molecular diagnostics |
| LDT | Laboratory developed test |
| LoD | Limit of detection |
| MRI | Magnetic resonance imaging |
| NGS | Next generation sequencing |
| NIPT | Non-invasive prenatal test |
| PCR | Polymerase chain reaction |
| PPV | Positive predictive value |
| PSA | Prostate specific antigen |
| RECIST | Response evaluation in solid tumours |
| SNP | Single nucleotide polymorphism |

# Notes



**Acknowledgements**
We would like to thank DAntes Design, Toronto, Canada for giving us permission to use her cell-free DNA illustration. For more details contact: *http://www.dantesdesign.ca/*

# Notes

# Disclaimer

*Hardman & Co provides professional independent research services and all information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable. However, no guarantee, warranty or representation, express or implied, can be given by Hardman & Co as to the accuracy, adequacy or completeness of the information contained in this research and they are not responsible for any errors or omissions or results obtained from use of such information. Neither Hardman & Co, nor any affiliates, officers, directors or employees accept any liability or responsibility in respect of the information which is subject to change without notice and may only be correct at the stated date of their issue, except in the case of gross negligence, fraud or wilful misconduct. In no event will Hardman & Co, its affiliates or any such parties be liable to you for any direct, special, indirect, consequential, incidental damages or any other damages of any kind even if Hardman & Co has been advised of the possibility thereof.*

*This research has been prepared purely for information purposes, and nothing in this report should be construed as an offer, or the solicitation of an offer, to buy or sell any security, product, service or investment. The research reflects the objective views of the analyst(s) named on the front page and does not constitute investment advice. However, the companies or legal entities covered in this research may pay us a fixed fee in order for this research to be made available. A full list of companies or legal entities that have paid us for coverage within the past 12 months can be viewed at http://www.hardmanandco.com/legals/research-disclosures. Hardman may provide other investment banking services to the companies or legal entities mentioned in this report.*

*Hardman & Co has a personal dealing policy which restricts staff and consultants' dealing in shares, bonds or other related instruments of companies or legal entities which pay Hardman & Co for any services, including research. No Hardman & Co staff, consultants or officers are employed or engaged by the companies or legal entities covered by this document in any capacity other than through Hardman & Co.*

*Hardman & Co does not buy or sell shares, either for their own account or for other parties and neither do they undertake investment business. We may provide investment banking services to corporate clients. Hardman & Co does not make recommendations. Accordingly, they do not publish records of their past recommendations. Where a Fair Value price is given in a research note, such as a DCF or peer comparison, this is the theoretical result of a study of a range of possible outcomes, and not a forecast of a likely share price. Hardman & Co may publish further notes on these securities, companies and legal entities but has no scheduled commitment and may cease to follow these securities, companies and legal entities without notice.*

*The information provided in this document is not intended for distribution to, or use by, any person or entity in any jurisdiction or country where such distribution or use would be contrary to law or regulation or which would subject Hardman & Co or its affiliates to any registration requirement within such jurisdiction or country.*

*Some or all alternative investments may not be suitable for certain investors. Investments in small and mid-cap corporations and foreign entities are speculative and involve a high degree of risk. An investor could lose all or a substantial amount of his or her investment. Investments may be leveraged and performance may be volatile; they may have high fees and expenses that reduce returns. Securities or legal entities mentioned in this document may not be suitable or appropriate for all investors. Where this document refers to a particular tax treatment, the tax treatment will depend on each investor's particular circumstances and may be subject to future change. Each investor's particular needs, investment objectives and financial situation were not taken into account in the preparation of this document and the material contained herein. Each investor must make his or her own independent decisions and obtain their own independent advice regarding any information, projects, securities, tax treatment or financial instruments mentioned herein. The fact that Hardman & Co has made available through this document various information constitutes neither a recommendation to enter into a particular transaction nor a representation that any financial instrument is suitable or appropriate for you. Each investor should consider whether an investment strategy of the purchase or sale of any product or security is appropriate for them in the light of their investment needs, objectives and financial circumstances.*

*This document constitutes a 'financial promotion' for the purposes of section 21 Financial Services and Markets Act 2000 (United Kingdom) ('FSMA') and accordingly has been approved by Capital Markets Strategy Ltd which is authorised and regulated by the Financial Conduct Authority (FCA).*

*No part of this document may be reproduced, stored in a retrieval system or transmitted in any form or by any means, mechanical, photocopying, recording or otherwise, without prior permission from Hardman & Co. By accepting this document, the recipient agrees to be bound by the limitations set out in this notice. This notice shall be governed and construed in accordance with English law. Hardman Research Ltd, trading as Hardman & Co, is an appointed representative of Capital Markets Strategy Ltd and is authorised and regulated by the FCA under registration number 600843. Hardman Research Ltd is registered at Companies House with number 8256259.*

*(Disclaimer Version 8 – Effective from August 2018)*

# Status of Hardman & Co's research under MiFID II

*Some professional investors, who are subject to the new MiFID II rules from 3rd January, may be unclear about the status of Hardman & Co research and, specifically, whether it can be accepted without a commercial arrangement. Hardman & Co's research is paid for by the companies, legal entities and issuers about which we write and, as such, falls within the scope of 'minor non-monetary benefits', as defined in the Markets in Financial Instruments Directive II.*

*In particular, Article 12(3) of the Directive states: 'The following benefits shall qualify as acceptable minor non-monetary benefits only if they are: (b) 'written material from a third party that is commissioned and paid for by a corporate issuer or potential issuer to promote a new issuance by the company, or where the third party firm is contractually engaged and paid by the issuer to produce such material on an ongoing basis, provided that the relationship is clearly disclosed in the material and that the material is made available at the same time to any investment firms wishing to receive it or to the general public…'*

*The fact that Hardman & Co is commissioned to write the research is disclosed in the disclaimer, and the research is widely available.*

*The full detail is on page 26 of the full directive, which can be accessed here: http://ec.europa.eu/finance/docs/level-2-measures/mifid-delegated-regulation-2016-2031.pdf*

*In addition, it should be noted that MiFID II's main aim is to ensure transparency in the relationship between fund managers and brokers/suppliers, and eliminate what is termed 'inducement', whereby free research is provided to fund managers to encourage them to deal with the broker. Hardman & Co is not inducing the reader of our research to trade through us, since we do not deal in any security or legal entity.*

research@hardmanandco.com

35 New Broad Street
London
EC2M 1NH

+44(0)20 7194 7622

www.hardmanandco.com