Zacks Small-Cap Research

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Aethlon Medical (AEMD-NASDAQ)

AEMD: NCI Cancer Grant, FDA's Use of "Real World Data"

AEMD continues to make substantive positive progress on several fronts. Using sum-of-the-parts valuation and based on current development progress in each respective category we place value of $90M for Hemopurifier in virus, pathogen, bioterror and cancer applications and combined value of ESI and ELLSA technology of $30M. Total company value equates to ~$120M or $8.00/share

Current Price (10/20/17)	$1.00
Valuation	**$8.00**

OUTLOOK

On Sept 12th AEMD announced that FDA approved AEMD's application seeking Expedited Access Pathway designation for their Hemopurifier with the following proposed indications for use; "The Hemopurifier is a single-use device indicated for the treatment of life-threatening highly glycosylated viruses that are not addressed with an approved treatment." This implies a fairly broad indication given its non-specificity to a particular virus, disease or condition as well as the fact that many of the highly glycosylated viruses lack an effective therapy.
On August 31, 2017 FDA finalized their draft guidance on the "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices". We do not know if the use of Real World Data is potentially on the table in designing a U.S. regulatory program for Hemopurifier or even if it is, if it can be of any benefit. But given the (effective) impossibility of conducting, for example, an RCT in Ebola, yet the lack of any serious treatment-related adverse events in any human application of Hemopurifier, coupled with the complete dearth of any drug or device that can effectively treat many of these glycosylated viruses and evidence that Hemopurifier can capture these substances, it makes sense to us that RWD will be (at least) under consideration. And if that is the case, it could help to define a feasible U.S. approval pathway.

SUMMARY DATA

52-Week High	**$5.17**
52-Week Low	**$0.90**
One-Year Return (%)	**-78.88**
Beta	**2.83**
Average Daily Volume (sh)	**499,257**
Shares Outstanding (mil)	**15**
Market Capitalization ($mil)	**$15**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**26**
Insider Ownership (%)	**19**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**N/A**
Industry	**Med-Hmo**

ZACKS ESTIMATES

Revenue
(in '000 of $)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2016	0.2 A	0.2 A	0.3 A	0.2 A	0.9 A
2017	0.0 A	0.4 A	0.0 A	0.0 A	0.4 A
2018	0.0 A	0.0 E	0.1 E	0.1 E	0.2 E
2019					0.1 E

Earnings per Share

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2016	-$0.18 A	-$0.16 A	-$0.16 A	-$0.16 A	-$0.66 A
2017	-$0.28 A	-$0.29 A	-$0.15 A	-$0.22 A	-$0.94 A
2018	-$0.21 A	-$0.16 E	-$0.12 E	-$0.11 E	-$0.57 E
2019					-$0.52 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW…

Secondary Offering Nets $5.3M, AEMD Regains NASDAQ Compliance

On October 4th AEMD closed on a secondary public offering of 5.4M shares at $1.10/share, with 100% warrant coverage (5yrs, $1.10 strike), for gross and net proceeds of $6.0M and $5.3M, respectively. Pro forma for the financing, fiscal Q1 2018 (ending June 30, 2017) cash balance would equal approximately $5.6M.

On August 1, 2017 AEMD received notice from NASDAQ that their stock would be de-listed from the exchange due to non-compliance of the ≥ $35M market cap requirement. The recent stock sale, however, allowed AEMD to regain NASDAQ under the alternative (5550b) requirement of having stockholder's equity of at least $2.5M.

Phase I NCI Grant for Isolation of Cancer-Related Exosomes

In mid-September AEMD announced that they scored a Phase I grant funded by the National Cancer Institute. The contract, dubbed "Device Strategy for Selective Isolation of Oncosomes and Non-Malignant Exosomes" is for $299,250. The University of Pittsburgh and Massachusetts General Hospital (researchers at Mass General were part of the tumor exosomes study discussed below) will work under AEMD to complete the contract which involves evaluation of AEMD's technology in the capture of circulating tumor-derived exosomes.

Hemopurifier For Cancer Treatment…

As a reminder, Aethlon has long been considering the potential role that Hemopurifier might play in treating cancer given evidence of its ability to capture tumor-derived exosomes. That interest has strengthened as of late given additional (published) evidence further supporting the role that circulating exosomes may play in tumor growth.

This includes an article titled, "Extracellular Vesicles: Emerging Target for Cancer Therapy" published in the April 2014 issue of the journal, Trends in Molecular Medicine. The article, written by researchers at Harvard Medical School, Massachusetts General Hospital and University of Oxford explores evidence that extracellular vesicles (i.e. - exosomes) play a key role in cancer development and progression and suppression of immune response. As such, extracellular vesicles (EVs) have increasingly become targets for anticancer therapy. This coincides with AEMD's cancer research and how Hemopurifier, via the removal of circulating cancer-secreted exosomes, could have utility in the treatment of cancer.

The authors also believe that EVs may also increase the body's resistance to cancer drugs and hinder their effectiveness. They further note that, while early evidence suggests that inhibition of EV biogenesis may have beneficial effects in the treatment of cancer, that a challenge has been to find therapies that can specifically target cancer-related EVs without affecting normal cell function. **The researchers specifically reference Hemopurifier as a potential therapy to overcome these challenges, noting that with the use of Hemopurifier "it might be possible** to specifically capture tumour cell-derived EVs on an antibody-coated matrix during extracorporeal dialysis. For example, in human epidermal growth factor receptor-2 (HER-2) overexpressing breast cancer, where HER-2-expressing EVs have been shown to interfere with therapy and are associated with tumour aggressiveness, anti-HER-2 antibodies could be used to remove HER-2-expressing EVs from circulation with the aim of improving therapeutic outcome. In principal, this approach could be tailored for other tumour types, as long as the tumour cell-derived EVs are enriched for tumour-specific proteins. However, whether the level and duration of EV depletion after ADAPT (i.e. - Hemopurifier) therapy would be sufficient to achieve a clinically relevant outcome remains to be determined."

The authors note that their current understanding of EVs role in cancer development and progression is still in the relatively early stages and is based on data from in vitro experiments. Their acknowledgement of Hemopurifier as potentially having utility in the treatment of cancer is also largely based on the supposition that removal of circulating EVs may be beneficial in interrupting the development and spread of tumors - which is still just a theory at this point. Nonetheless, we think this research does add meaningful credibility to Hemopurifier's potential role in cancer suppression and adds additional support to AEMD's research which indicates the same.

In addition, the NCI grant is also an early, yet potentially substantive step towards additional acknowledgement of tumor-derived exosomes' role in cancer and validation of Hemopurifiers' ability in capturing the substances.

FDA Grants EAP Designation For Hemopurifier in Treatment of Life-Threatening Diseases

On September 12th AEMD announced that FDA approved AEMD's application seeking Expedited Access Pathway designation for their Hemopurifier with the following proposed indications for use; "The Hemopurifier is a single-use device indicated for the treatment of life-threatening highly glycosylated viruses that are not addressed with an

approved treatment." This implies a fairly broad indication given its non-specificity to a particular virus, disease or condition as well as the fact that many of the highly glycosylated viruses lack an effective therapy.

As a refresher, viruses use glycosylation as a means to avoid detection by the body's immune system. Highly glycosylated viruses, such as HIV, HCV, Ebola, West Nile and pandemic flu strains (among a host of others) have proven to be particularly resilient and difficult to treat. The filter within the Hemopurifier contains galanthus nivalis agglutinin (GNA) which binds to the glycan shield of these viruses, thereby removing it from the bloodstream prior to the toxins infecting other cells or organs.

While we had anticipated that FDA would approve the EAP pathway, confirmation of that is nonetheless a significant event given the benefits of the program. Management noted during a presentation at BIO Investor Forum earlier this week that since receiving notice of EAP designation, the company has been in contact with FDA, including with the personnel that will be working directly with them. AEMD expects to schedule an in-person meeting with FDA in the near-term.

FDA Finalizes Guidance on Real-World Data For Regulatory Decision-Making

On August 31, 2017 FDA finalized their draft guidance (issued July 27, 2016) on the "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices". The document is available here (http://bit.ly/2xDKXG1).

While randomized, controlled studies (RCTs) will almost certainly remain the gold-standard for approving most Class III (i.e. high-risk) or other devices that are mandated to follow FDA's PMA pathway, the agency has recently begun to embrace the idea of using "real world data" (RWD) and "real world evidence" (RWE) to make approval and other regulatory decisions. In 2015 FDA approved more than eight new medical devices and expanded the label on several others through supporting RWD – this included several high-risk, implantable devices.

FDA's recent move towards greater acceptance of RWD in decision-making has to do, in part, with the idea that traditional clinical trials are too rigid in some circumstances as well as the fact that "traditional clinical trial(s) may be impractical or excessively challenging to conduct" (as AEMD's might be for highly virulent viruses). That could mean that (for example), in lieu of a randomized clinical trial, the sponsor may be allowed to use an existing database or medical registry as the control arm for a pivotal study.

FDA's recently appointed commissioner Dr. Scott Gottlieb's remarks to The National Academy of Sciences on September 19, 2017 provide some additional insight into the regulators' thoughts towards greater application of RWD and RWE in their decision-making processes. While the full text can be found here (http://bit.ly/2yJG4ex), some of the highlights include:

- "The hierarchy of evidence is evolving as a consequence. This is the hierarchy that has long defined the reliability of clinical evidence, and puts the randomized, prospective, placebo controlled trial at the top of that pyramid. This pyramid has remained unchanged, even as our tools for collecting practical data have advanced; even as the constructs that fall underneath the fully randomized, prospective, placebo-controlled trial are expanding, and their usefulness for informing our decisions becoming more apparent; even as the reliability of other forms of evidence is increasing as the methodologies for evaluating different forms of data continue to improve. That includes RWE."
- "FDA needs to think of itself as a curator of information. Not just an arbiter, where a single truth standard is secured to a fixed orthodoxy. The latter concept is increasingly at odds with the way decisions are being made by others who depend on reliable evidence to guide their paths, including doctors and health plans. FDA is often an important, independent evaluator of information."
- "The fact is there's often no single truth standard when it comes to the evidence used to support medical decisions. Clinical choices are made all the time, based on a mosaic of information of various precision and certainty. That continuum includes real world evidence, as well as the facts gleaned from rigorous and carefully fashioned trials...and a lot of evidence constructs in between."
- "…there's nothing in our statute or regulations that prevent FDA from using a broad range of informative sources of evidence. On the contrary, many of our statutory responsibilities boil down to one principal calculus: What do we know, and how do we balance benefits and risk based on the fullest possible information."
- "For those who'd challenge the suitability of our effort to incorporate real world evidence into our regulatory model, I'd challenge you with the opposite intention: Should a product be marketed based on a data set that speaks to a limited and rigidly constructed circumstance, when the clinical use, and in turn the evidence we might have to evaluate the product, could have been far richer, far more diverse, and more informative?"

- "That means embracing the full continuum of evidence that informs their [i.e. novel medical devices] clinical use. We see this approach gaining more rapid and widespread acceptance when it comes to some medical products. But we need to continue to more widely advance this life cycle concept of regulation."

Could RWD Facilitate and Help Define Hemopurifier's FDA Pathway?...
As we have noted in our recent coverage of AEMD, we expect Hemopurifier will be required to follow a PMA pathway under the recently designated EAP program and expect this will require clinical trials. Yet, as we have also noted, the next-steps towards validation are largely unknown given that it is not feasible to conduct clinical studies for targets such as highly virulent viruses or pandemic threats. The benefits of EAP designation, particularly AEMD's ability to have earlier and more significant involvement with regulators – can be of great help in designing an appropriate validation program.

We do not know if the use of Real World Data is potentially on the table in designing a U.S. regulatory program for Hemopurifier or even if it is, if it can be of any benefit. But given the (effective) impossibility of conducting, for example, an RCT in Ebola, yet the lack of any serious treatment-related adverse events in any human application of Hemopurifier, coupled with the complete dearth of any drug or device that can effectively treat many of these glycosylated viruses and evidence that Hemopurifier can capture these substances, it makes sense to us that RWD will be (at least) under consideration. And if that is the case, it could help to define a feasible U.S. approval pathway.

Production Capabilities Secured

Perhaps an indication of management's expectations of eventual commercialization, earlier this week Aethlon announced a formal collaboration with iBio, Inc (IBIO), a plant-based biopharmaceuticals company, to provide (as-needed) large-scale production of the plant-derived lectin (a recombinant form of Galanthus nivalis agglutin, or GNA) housed within the Hemopurifier cartridge that captures circulating viruses from the blood.

As a reminder, Aethlon had noted during their U.S. feasibility study that they had leveraged their contract with DARPA to fund current good manufacturing practice (cGMP) systems for the production of the Hemopurifier. The DARPA grant included two manufacturing-specific milestones – the first of which AEMD completed during year-three of the contract and the other which they completed during year-four.

AEMD's recent press release mentions that they have completed a study with iBio, confirming their ability to produce GNA under cGMP. Per iBio's website, their CDMO development and manufacturing facility, located near Houston, is capable of growing over four million plants as "in process inventory". The large-capacity facility is also capable of meeting high production quotas which could be important, particularly in the event of high on-demand need such as, for example, if Hemopurifier was cleared for use as a countermeasure against certain pandemic outbreaks.

Valuation

We have updated our valuation to account for the higher share count (relative to our forecast) as a result of the recent financing.

Using sum-of-the-parts valuation and based on current development progress in each respective category we place value of $90M for Hemopurifier in virus, pathogen, bioterror and cancer applications and combined value of ESI and ELLSA technology of $30M. As such, we value AEMD at approximately $120M or ~$8.00/share.

PROJECTED INCOME STATMENT

Aethlon Medical, Inc.

	2015 A	2016 A	Q1 A	Q2 A	Q3 A	Q4 A	2017 A	Q1 A	Q2 E	Q3 E	Q4 E	2018 E	2019 E
Revenue	$762.4	$886.6	$4.6	$387.4	$0.0	$0.0	$392.1	$0.0	$20.0	$89.0	$89.0	$198.0	$101.0
YOY Growth	*-53.0%*	*16.3%*	*-97.6%*	*105.7%*	*-100.0%*	*-100.0%*	*-55.8%*	*-100.0%*	*-94.8%*	-	-	*4171.8%*	*-73.9%*
Cost of Goods Sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$762.4	$886.6	$4.6	$387.4	$0.0	$0.0	$392.1	$0.0	$20.0	$89.0	$89.0	$198.0	$101.0
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	-	-	*100.0%*	-	-	-	-	-	-
SG&A	$3,727.7	$4,489.4	$1,018.3	$2,333.3	$1,057.1	$1,408.8	$5,817.4	$1,002.8	$1,202.0	$1,201.0	$1,309.0	$4,714.8	$6,812.0
%SG&A	*488.9%*	*506.4%*	*21969.5%*	*602.2%*	-	-	*1483.8%*	-	-	-	-	-	-
R&D	$1,027.6	$782.0	$118.0	$280.9	$178.4	$95.7	$673.0	$157.5	$176.0	$241.0	$355.0	$929.5	$2,160.0
%R&D	*134.8%*	*88.2%*	*2545.8%*	*72.5%*	-	-	*171.7%*	-	-	-	-	-	-
Impairment	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($3,992.8)	($4,384.8)	($1,131.7)	($2,226.7)	($1,235.5)	($1,504.5)	($6,098.4)	($1,160.2)	($1,358.0)	($1,353.0)	($1,575.0)	($5,446.2)	($8,871.0)
Operating Margin	-	*-494.6%*	-	-	-	-	*-1555.4%*	-	-	-	-	-	-
Loss on extinguishment of debt	$2,754.0	$0.0	$616.9	$0.0	($58.7)	$0.0	$558.2	$376.9	$0.0	$0.0	$0.0	$376.9	$0.0
(Gain)/loss on derivative liability	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$119.8	$0.0	$0.0	$0.0	$119.8	$0.0
Interest (income), net	$452.3	$573.8	$42.2	$36.6	$36.6	$189.0	$304.3	$188.6	$104.0	$101.0	$99.0	$492.6	$375.0
Other expense	($219.6)	$0.0	$345.8	$0.0	$0.0	$0.0	$345.8	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($6,979.5)	($4,958.6)	($2,136.5)	($2,263.3)	($1,213.4)	($1,693.5)	($7,306.7)	($1,845.6)	($1,462.0)	($1,454.0)	($1,674.0)	($6,435.6)	($9,246.0)
Taxes (benefit)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	($6,797.2)	($4,872.4)	($2,128.8)	($2,255.6)	($1,205.7)	($1,686.0)	($7,276.1)	($1,841.8)	($1,462.0)	($1,454.0)	($1,674.0)	($6,431.8)	($9,246.0)
Net Margin	*-891.5%*	*-549.6%*	-	-	-	-	*-1855.8%*	-	-	-	-	*-3248.4%*	*-9154.5%*
EPS	($1.22)	($0.66)	($0.28)	($0.29)	($0.15)	($0.22)	($0.94)	($0.21)	($0.16)	($0.12)	($0.11)	($0.57)	($0.52)
YOY Growth	*-64.7%*	*-45.8%*	-	-	-	-	*42.2%*	-	-	-	-	*104.2%*	*78.1%*
Diluted Shares O/S	5,594	7,394	7,622	7,757	7,927	7,751	7,764	8,806	8,987	12,232	15,080	11,276	17,855

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Appendix

U.S. Feasibility Study HCV Capture Data Announced at BIO International Convention
During a presentation at the 2017 BIO International Convention in San Diego on June 21st management announced HCV capture data from their recently completed U.S. feasibility study. As a reminder, eight patients with ESRD and infected with HCV were enrolled in the single-arm study, which was conducted at DaVita MedCenter in Houston. Subjects received Hemopurifier treatment 3x/week for two consecutive weeks. Data related to vital signs, blood work, hematology and liver function were collected during the weeks of Hemopurifier treatment as well as one week prior. So while this was primarily a safety study, efficacy-related data including viral load reductions and measurement of total virus captured were also collected and are expected to be included in the final report submission to FDA.

Relative to the primary endpoint (i.e. safety), Aethlon announced earlier that Hemopurifier treatment was well-tolerated and that there were no device-related adverse events reported. Given that safety was the main objective of the study and these patients (i.e. those with ESRD and HCV) were of highly compromised health, the positive safety outcome is significant not only in terms of the event-profile of the device, but also as solid support in petitioning FDA for follow-on clinical trials as well as for (potentially immediate) consideration under PHEMCE's broad-spectrum countermeasure program mandate.

As it relates to the (secondary) efficacy measures, the BIO presentation gave us the first glimpse on viral capture during the feasibility study. Capture data that was presented relates to measurements taken following two (of the six total) Hemopurifier treatments. Data was available from 13 cartridges related to seven patients (two cartridges from six patients and one cartridge from one patient). As the slides from the presentation (below) show, virus capture ranged from a low of 589k I.U. (patient six, cartridge two) to a high of 1.62B (patient one, cartridge two). Average capture per cartridge was 154.4M. Management noted during the presentation that the study researchers mistakenly (i.e. violated study protocol) thoroughly saline-washed the cartridges at the treatment site following Hemopurifier treatment (and prior to measuring capture data) which could have had the effect of reducing the capture yields.

While its difficult to judge the clinical significance of this data, it does clearly show that the Hemopurifier is capturing the HCV virus (which may have been even greater if not for the saline-wash issue). This adds to the considerable prior evidence of Hemopurifier's ability to capture target substances including human studies in HIV and Ebola (as well as earlier human studies in HCV) and in vitro studies in a host of other viruses.

Values measured post 500 ml/min high pressure saline wash

DaVita Med Center Dialysis Virus Capture Study
Houston, Texas USA / HCV-Infected ESRD Subjects / 4-Hour Treatment

Patient Cartridge Code	IU Capture Value	Total Virus Capture
01-V1*	N/A	N/A
01-V2	1.62×10^9	1,620,000,000
02-V1	3.99×10^6	3,990,000
02-V2	1.18×10^7	11,800,000
* Assay protocol deviation / improper storage and loss of elution fluid		
03-V1	1.38×10^7	13,800,000
03-V2	1.29×10^7	12,900,000
04-V1	1.24×10^8	124,000,000
04-V2	6.38×10^7	63,800,000
05-V1	4.19×10^7	41,900,000
05-V2	7.10×10^6	7,100,000
06-V1	1.71×10^6	1,710,000
06-V2	5.89×10^5	589,000
07-V1	2.84×10^6	2,840,000
07-V2	1.03×10^8	103,000,000
	Average Virus Capture	154,418,000

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CTE Study Refresher…

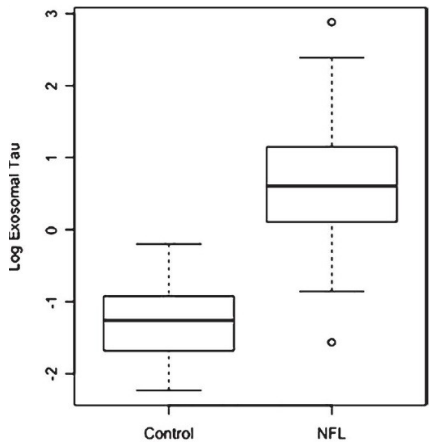
As a reminder, Aethlon's majority-owned subsidiary Exosome Sciences (ESI) has collaborated with Boston University's CTE Center for the development of a blood-based diagnostic that would be able to identify CTE in living individuals. ESI has used what they learned in how to isolate certain brain-specific biomarkers to evaluate blood/plasma samples collected by participants (former NFL players and a control group) enrolled in BU's DETECT study. The study is the first on CTE funded by the NIH.

In April 2015 investigators presented initial findings of DETECT at the annual Traumatic Brain Injury Conference held in Washington, DC. Results were from 78 former NFL players and 16 controls and showed that the NFL players had significantly higher levels of tausome (tau) in their blood/plasma than those of the controls (subsequent to release of these preliminary results, additional analysis (per the company's comments) showed that TauSome levels were approximately 9 times higher, on average, in the NFL group as compared to control subjects). Tau levels were also correlated to performance on cognition tests, with higher tau levels corresponding to poorer test performance.

A manuscript of the preliminary results were published in the online version of the Journal of Alzheimer's Disease in early 2016. Inclusion criteria for the NFL group included age 40-69, a minimum of 12 years of tackle football including a minimum of 2 years in NFL at position associated with extensive head impacts and a self-report of having symptoms associated with CTE including changes in cognition, behavior and mood. Inclusion criteria for control included male age 40-69, minimum of 4 years in non-contact sports including 2 at college level or higher.

The publication provided additional details of the results which included (all charts and graphics[1]);

- Total plasma exosomes did not differ between the NFL and control groups and NFL did have significantly higher (p<0.0001) plasma exosomal tau (results in figure below are unadjusted for age). Per management's comments, additional analysis done subsequent to this preliminary data found that tau levels were approximately nine times higher in the NFL group as compared to the control group



- Plasma exosome levels were still statistically significantly higher (p<0.0001) in the NFL group than in control after adjusting for age and body mass (BMI)

Parameter estimates of ANCOVA for exosomal tau

Predictor	Estimate	Standard Error	*t*-test	*p*-value
Difference of control minus NFL exosomal tau levels	–1.93	0.24	–8.05	<0.0001
Age	0.01	0.01	1.20	0.2351
Body Mass Index	0.01	0.02	0.34	0.7319

[1] Preliminary Study of Plasma Exosomal Tau as a Potential Biomarker for Chronic Traumatic Encephalopathy. Stern, Robert A. et al. Journal of Alzheimer's Disease, vol. Preprint, no. Preprint, pp. 1-11, 2016

- The diagnostic demonstrated 82% sensitivity with 100% specificity, 100% positive predictive value and 53% negative predictive value. In other words, all of the elevated tau results came from NFL players, although not all NFL players showed elevated tau levels

- In the NFL cohort, tau levels were statistically significantly inversely correlated to performance on cognition tests (Wechsler Adult Intelligence Scale Digital Symbol and Neuropsychological Assessment Battery List Learning)

- While exosomal tau was statistically correlated to cognition, it was not correlated to any of the mood or behavioral measures

Relationship between log exosomal tau and measures of cognition, mood, and behavior from mixed effects regression analysis adjusted for age and education as well as for associations of multiple tests per subject and correlations of tests within the same domain for the NFL group only

Domain and Measure	Partial Correlation	Beta Estimate	Standard Error	t-test	p-value
Psychomotor Speed					
Wechsler Adult Intelligence Scale-Revised [78] Digit Symbol Test, Raw Score	–0.33	–3.01	1.16	–2.60	0.0093
Trail Making Test [79] Part A, T-Score	–0.18	–2.03	1.52	–1.33	0.1826
Executive Functioning					
Trail Making Test [79] Part B, T-Score	–0.03	–0.11	2.15	–0.05	0.9589
Wisconsin Card Sorting Test [80] Percent Errors, T-score	–0.09	–0.74	1.28	–0.58	0.5605
Rey-Osterreith Complex Figure –Boston Qualitative Scoring System (BQSS) [81] Organization Score, T-score	0.09	1.69	2.06	0.82	0.4117
Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A) [82] Metacognition Index, T-score	0.01	0.34	1.75	0.20	0.8434
Learning and Memory					
BQSS [81] Immediate Presence & Accuracy, T-score	–0.14	–1.14	1.32	–0.86	0.3879
BQSS [81] Delayed Presence & Accuracy, T-score	–0.19	–1.74	1.44	–1.21	0.2258
Neuropsychological Assessment Battery (NAB) [83] List Learning Test List A Immediate Recall, T-score	–0.31	–2.84	1.14	–2.50	0.0126
NAB [83] List Learning Test List A Short Delay Recall, T-score	–0.29	–3.41	1.63	–2.09	0.0365
NAB [83] List Learning Test List A Long Delay Recall, T-score	–0.30	–4.35	1.78	–2.44	0.0147
Visuospatial Skills					
NAB [83] Map Reading Test, T-score	0.11	1.38	1.25	1.10	0.2709
Language					
NAB [83] Naming Test, T-Score	–0.12	–1.41	1.46	–0.97	0.3336
Mood					

Key Takeaways:

- ESI's tau diagnostic demonstrated
    - o exosome tau was significantly higher (~9x) in NFL players than in control
    - o exosome tau was significantly higher (~10x) in Alzheimer's patients than in control
    - o exosome tau was significantly correlated to performance on cognition tests. Higher levels of tau correlated to poorer test performance on memory and psychomotor speed tests

- Exosome tau was not correlated to mood or behavior measures

- Highest levels of tau were found only in NFL players although not all NFL players had high levels of tau
- Confirmation that the diagnostic can accurately identify individuals with CTE would require neuropathological examination of the brain

Relative to the lack of association between tau levels and mood/behavior test results, the investigators noted that there is evidence suggesting tau is a better indicator of cognitive function than it is of mood/behavior and that CTE-related cognitive functionality impairments have been reported to be more prevalent in later stage of the disease as compared to mood/behavior changes. In addition, they note "It is possible that the mood and behavioral features may have multiple potential etiologies, in addition to CTE-associated tau degeneration, whereas the cognitive changes are more consistently due to the tau degeneration."

Relative to the fact that not all NFL players had high levels of tau – the investigators indicated that this was not a surprise as it should be expected that not all NFL players, even those in the study (i.e. – which have at least some symptoms), would have CTE.

While the investigators concluded that these findings suggest exosomal tau in plasma may be an accurate biomarker for CTE, additional research needs to be done. They note some limitations of the study including that;
- confirmation of association between exosome tau and CTE would require a neuropathological exam
- the study did not include markers for where the tau originated so there was not complete confidence that these were all brain-derived exosomes (tau is also present in other areas of the body besides the brain)
- and if these were brain-derived exosomes, the study was also not powered to differentiate between where in the brain they came from (i.e. – neuronal vs, non-neuronal, which may have implications)
- small sample size of the study (particularly control)
- lack of an additional biomarker for CTE

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