EXECUTIVE SUMMARY

THE PROBLEMS: In Canada, the USA and Australia 20% of the population suffers from a mental illness. In these countries 9% to 14% of all adults take an antidepressant medication (ADM) and suicide is a leading cause of death. While good psychiatric training and clinical experience are crucial determinants of outcome, current "best practice" management is driven entirely by clinical interview and observation. In the absence of validated biomarkers, diagnosis is often inaccurate and delayed[1]. As an example the diagnosis of bipolar disorder is only correctly made until, on average, 5 years of symptoms and 4 psychiatric assessments have been done [2]. Decisions about effective treatment are inefficient and made largely through serial trial and error. Suicide risk assessment is highly inaccurate. A scientific review of all suicide risk assessment methods over the last 50 years of research concluded that "prediction was only slightly better than chance"[3]. In the large American Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial only 37% of the roughly 4000 depressed patients studied reached full remission during the first round of antidepressant medication treatment[4]. The startling inefficiencies of current "best practice" lead to much avoidable suffering, lost workplace productivity, increased healthcare costs and death by suicide.

OUR SOLUTION: Digital Medical Experts Inc (DME) has developed artificial intelligence algorithms (AIAs) that can dramatically improve management effectiveness by providing clinicians with the results of analysis of the complex electrical activity patterns (EEG) generated by the brain during health and disease. Our pattern recognition software classifies an individual according to diagnosis, response to treatment and suicide risk category, based solely on the individual's EEG profile and generates an electronic report can be used to develop a personalized treatment plan based upon each person's unique brain activity pattern. As an example, after learning that the probability of good response is similar for both forms of treatment, a patient may prefer psychotherapy over the inconvenience and side effects of medications.

HOW OUR SYSTEM WORKS: Our suite of AIAs have been trained using data collected from over 2000 patients and healthy volunteers (see Appendix 1). These data include EEG and information on I) diagnosis, ii) personality, iii) social support, iv) symptom severity, v) physical and mental disability, vi) cognitive functioning and vii) suicide risk, viii) response to different forms of treatment. Our AIAs search these data for patterns that can be used to accurately determine the diagnosis, treatment response profile and suicide risk for each new patient within minutes.

DIAGNOSIS: Our AIA's deliver psychiatric diagnoses showing over 90% agreement with the diagnoses rendered by a psychiatrist-led clinical consensus team using DSM diagnostic criteria and standardized diagnostic interview. Distinguishing bipolar disorder-depressed phase (BD-D) from MDD can be a highly challenging task. Studies suggest that this is typically not achieved until the individual has been under treatment for 6-8 years [1]. Our algorithms have been trained to distinguish subjects with MDD from those with BD-D and other conditions such as schizophrenia with 90 % accuracy using a single EEG[5, 6] . In patients with unrecognized bipolar depression, antidepressants can induce switch to (hypo)mania, cause mixed symptoms, or increase the risk of suicide.

TREATMENT RESPONSE: Our AIAs generate treatment response profiles which predict response to specific forms of treatment with accuracy levels that significantly exceed those of an expert psychiatrist. In contrast with the 33% remission rate seen with current best practice methodology our AIAs can generate accuracy of 79-90% in the prediction of response to ADMs[7, 8], the antipsychotic clozapine[9, 10], cognitive behaviour psychotherapy, and brain stimulation therapy such as repetitive transcranial magnetic stimulation [11] and even placebo medication[8]. Placebo response prediction would be of great interest to pharmaceutical companies doing clinical trials of new psychotropic medications. Our work with ADM prediction has been independently confirmed by independent researcher groups [12, 13] and by met analyses[14] . We estimate that our technology will generate savings of over $4000 in medical costs and $8000 in income replacement costs for each person treated for MDD or bipolar disorder. (see Appendix 2).

ASSESSING SUICIDE RISK: Our newest technology could significantly reduce death by suicide. Using current methods even the skilled clinician cannot predict suicide with much better than 50 % accuracy (reference 2). In contrast our AIAs can detect suicidal ideation with 70 -80% accuracy. Using questionnaire data collected from 800 military veterans our AIAs detected suicidal thinking with 75% accuracy [15]. In a pilot study in 68 persons with MDD, our AIAs detected suicidal ideation with over 70% accuracy using only EEG data (unpublished). We are currently analyzing newly acquired EEG data from over 200 subjects to further refine our algorithms for better discrimination.

PROVIDING EXPERT ADVICE REMOTELY: In the USA, Canada and Australia there are 277,000 primary care physicians but only 58,500 psychiatrists. In the USA most of the 21 million mental health visits annually occur in the primary care setting. Portable EEG headsets and cloud-based data transfer protocols we have already operational would allow our technology to be used in any primary care office setting with internet access, including those in remote and under-serviced locations. In our test cases we have been able to provide a digital report within 1 hour of receiving the EEG data. We have created a consumer version of our technology intended for use by Universities, the Military and Industry to screen for mental illness and suicide risk.

PATENT PORTFOLIO

DME has been allowed patents in Canada (Canadian patent website), the USAhttps://patents.google.com/patent/WO2009103156A1/en, Australia (see Aust patent website)

AWARDS and RECOGNITION

2014, September 14: Canadian Psychiatric Association Annual Meeting, Toronto, Ontario, Canada:

Representing Digital Medical Experts, Dr Hasey receives the 1st Place R.O. Jones Award for Best Paper. Title: *Building a Virtual Psychiatrist: Using Digital Technology to Assist With Diagnosis and Treatment Planning.* https://www.newswire.ca/news-releases/psychiatrists-recognize-outstanding-contributions-to-mental-health-at-their-annual-conference-515619411.html

2017, 25-28 October, 35th Brazilian Congress of Psychiatry, Sao Paulo, Brazil:
Representing Digital Medical Experts, Dr Hasey delivers a **keynote address** entitled: "Developing Artificial Intelligence Tools for Diagnosis and Treatment of Mood Disorders and Schizophrenia" http://www.cbpabp.org.br/english/?p=3221

2017, November 29-30, John H. Chapman Space Centre, Saint-Hubert, Quebec, Canada:
Representing Digital Medical Experts, Dr Hasey presents on "**Transforming Healthcare through Artificial Intelligence"** at the Canadian Space Agency meeting entitled "**Planning Canada's next chapter in human space exploration: health and biomedical roles",** (see http://www.asc-csa.gc.ca/eng/events/2017/planning-canada-next-chapter-human-space-exploration-health-and-biomedical-roles.asp for program see http://www.asc-csa.gc.ca/pdf/eng/events/2017/planning-forum-program.pdf**)**

2018, October 10, Paris, France:
Digital Medical Experts is one of the first North American Companies to win the **Universal Biotech Innovation Prize** (Digitech category) offered by France's Universal Biotech group
http://www.universal-biotech.com/wp-content/uploads/2018/10/2018-10-Communique-de-presse-EN-compressed.pdf

2018, November 29–30, Embassy of Canada to the United States, Washington, D.C.:
Digital Medical Experts addresses the North Atlantic Treaty Organization (NATO) **North Atlantic Treaty Organization Human Factors and Medicine (HFM)** section title . Leveraging Technology in Military Mental Health Big Data & Machine Learning, Meeting #4 see https://www.cstsonline.org/assets/media/documents/NATO_Program_Nov29_30_2018.pdf

2019 March 23
Digital Medical Experts receives the top score in the information technology category at the Sci Innovation China-CANADA competition at Toronto City Hall and is among the 20 (out of 200) Canadian companies invited to present their technology in Shenzhen China. https://www.lawtimesnews.com/news/general/gowlings-advises-2019-sci-innovation-competition-winner/266865

2020 October
Digital Medical Experts is accepted as a company to be mentored by the Creative Destruction Laboratory https://www.creativedestructionlab.com

2022 October 10
DME Scientists M Ravan and G Hasey are interviewed by IEEE Spectrum. Published article entitled "AI Can Offer Insight Into Who Responds to Antidepressants https://spectrum.ieee.org/at-last-insight-into-who-responds-to-anti-depressants

2022 Nov 21
Digital Medical Experts advances to tier 2 in the Sci Innovation China-CANADA entrepreneurial competition

1. Baldessarini, R.J., G.H. Vazquez, and L. Tondo, *Bipolar depression: a major unsolved challenge.* Int J Bipolar Disord, 2020. **8**(1): p. 1.
2. Keramatian, K., et al., *Clinical and demographic factors associated with delayed diagnosis of bipolar disorder: Data from Health Outcomes and Patient Evaluations in Bipolar Disorder (HOPE-BD) study.* J Affect Disord, 2022. **296**: p. 506-513.
3. Franklin, J.C., et al., *Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research.* Psychol Bull, 2017. **143**(2): p. 187-232.
4. Warden, D., et al., *The STAR*D Project results: a comprehensive review of findings.* Curr Psychiatry Rep, 2007. **9**(6): p. 449-59.
5. Ravan, M., et al., *Discriminating between bipolar and major depressive disorder using a machine learning approach and resting-state EEG data.* Clin Neurophysiol, 2023. **146**: p. 30-39.
6. Khodayari-Rostamabad, A., et al., *Diagnosis of psychiatric disorders using EEG data and employing a statistical decision model.* Annu Int Conf IEEE Eng Med Biol Soc, 2010. **2010**: p. 4006-9.
7. Khodayari-Rostamabad, A., et al., *A machine learning approach using EEG data to predict response to SSRI treatment for major depressive disorder.* Clin Neurophysiol, 2013. **124**(10): p. 1975-85.
8. Oakley, T., et al., *EEG Biomarkers to Predict Response to Sertraline and Placebo Treatment in Major Depressive Disorder.* IEEE Trans Biomed Eng, 2022. **PP**.
9. Ravan, M., et al., *A machine learning approach using auditory odd-ball responses to investigate the effect of Clozapine therapy.* Clin Neurophysiol, 2015. **126**(4): p. 721-30.

10. Khodayari-Rostamabad, A., et al., *A pilot study to determine whether machine learning methodologies using pre-treatment electroencephalography can predict the symptomatic response to clozapine therapy.* Clin Neurophysiol, 2010. **121**(12): p. 1998-2006.
11. Khodayari-Rostamabad, A., et al., *Using pre-treatment electroencephalography data to predict response to transcranial magnetic stimulation therapy for major depression.* Conf Proc IEEE Eng Med Biol Soc, 2011. **2011**: p. 6418-21.
12. Mumtaz, W., et al., *A wavelet-based technique to predict treatment outcome for Major Depressive Disorder.* PLoS One, 2017. **12**(2): p. e0171409.
13. Wu, W., et al., *An electroencephalographic signature predicts antidepressant response in major depression.* Nat Biotechnol, 2020. **38**(4): p. 439-447.
14. Cohen, S.E., et al., *Electroencephalography for predicting antidepressant treatment success: A systematic review and meta-analysis.* J Affect Disord, 2023. **321**: p. 201-207.
15. Colic, S., He, J.C., Richardson, J.D., St Cyr, K.; Reilly, J.; Hasey, G., *A Machine Learning Approach to Identification of Self Harm and Suicidal Ideation in Military and Police Veterans.* Journal of Military, Veteran and FAMILY Health. **8**(1): p. 56-67.

Appendix 1 (Training database)

PRIMARY VARIABLES	STUDY TYPE		NUMBER OF SUBJECTS
Standardized diagnosis plus 20-48 lead EEG with eyes open and eyes closed	Machine learning analysis of EEG data to make diagnosis (Diagnosis and EEG data)	**DIAGNOSIS DATA**	
		Major depressive Disorder (MDD)	169
		MDD atypical	27
		MDD psychotic	35
		Bipolar disorder-depressed phase	84
		Bipolar disorder- manic Phase	49
		Schizophrenia	163
		Healthy Volunteers	308
Standardized diagnosis plus treatment response data including mood rating scales plus 20 lead EEG with eyes open and eyes closed	Machine learning analysis of EEG to predict Treatment response (Diagnosis, treatment response, suicide and EEG data)	**TREATMENT TYPE**	
		SSRI antidepressants	22
		Repetitive Transcranial Magnetic Stimulation	82
		Clozapine	37
		Cognitive Behaviour Therapy	22
		Electroconvulsive therapy	11
Standardized diagnosis plus treatment response data including mood rating scales plus 20 lead EEG with eyes open and eyes closed	Diagnosis, treatment response suicide and EEG data	Sertraline bupropion or placebo	238
Test battery including, MINI, HVLT, RBANS, long form of the PAI, WHODAS and Beck Depression rating scale pre and post ECT	Machine learning analysis of pre-treatment cognition and personality to predict side effects and response to ECT (Diagnosis, treatment response and suicide data)	Electroconvulsive therapy	120
SF-36, PHQ, PCL-Vs., History re Deployment, trauma, alcohol/drug abuse, supports, psych symptoms	Detect Suicidal ideation Using questionnaire data (Diagnosis and suicide data)	Various therapies	821
TOTAL NUMBER OF INDIVIDUAL SUBJECTS IN ABOVE DATABASE			**2188**

Appendix 2 (Insurance savings)

Insurance Company Treatment Cost Estimates Related to Antidepressant Treatment for Major Depressive and Bipolar Depressive Disorders

Disability Claimant Assumptions		
Annual salary	$55,000	Canadian avg salary for 2020
Share of salary paid by insurer	66%	Assumption
Weekly disability payments	$698	
Mood Disorder Prevalence and Diagnosis Accuracy [1]		
Number of claimants	165,000	Estimated depressive disability claimants (Can)
...with major depressive disorder (MDD)	116,875	(71%)
...with bipolar depressive disorder (BDD)	48,125	(29%)
BDD Cases Diagnosed Correctly		
...using current industry methods [2]	35%	probability
...using DME methods [3]	79%	probability
Additional treatment time with misdiagnosis [4]	15	weeks
Prescribed Treatment Effectiveness		
...using current industry methods [5]	46.0%	response rate
...using DME methods [6]	87.9%	response rate
Prescription Drug and Medical Costs (Full Treatment Cycle)		
...with correct diagnosis and treatment plan [7]	$6,656	per person
...with continued treatment trial and error [8]	$17,119	per person

Average Weeks on Disability	MDD	BDD
Current industry methods [9]	9.2	19.0
DME method with treatment recommendation [10]	4.5	12.4

Annual Savings per 165,000 Claimants Diagnosed with Depression

Income Replacement Cost Savings	Avg. Weeks On Disability	Cost per Claimant	DME Method Savings	
			Per Claimant	Total
Current industry methods	12.0	$8,407		
DME method with treatment recommendation	6.8	$4,750	**$3,658**	**$603,509,315**

Prescription Drug and Medical Cost Savings	Treatment Effectiveness	Cost per Claimant	DME Method Savings	
			Per Claimant	Total
Current industry methods	46%	$12,306		
DME method with treatment recommendation	88%	$7,922	**$4,384**	**$723,359,505**

TOTAL Income Replacement AND Prescription Drug and Medical Cost Savings	Cost per Claimant	DME Method Savings		
		on Disability	per Claimant	Total Cost Savings
Current industry methods	$20,713			
DME method with treatment recommendation	$12,672	5.2	**$8,042**	**$1,326,868,820**

Footnotes

1) Based on mood disorder prevalence data in the US: 6.8% of the population with MDD and 2.8% with BD (Harvard Medical School, 2007. National Comorbidity Survey).
2) 60 to 70 % of patients with BDD are misdiagnosed as MDD (Altamura, Buoli et al. 2015, Nasrallah 2015, Shen, Zhang et al. 2018)
*3) Number of weeks is a weighted average based on STAR*D study (Warden, D., et al., "The STAR*D Project results: a comprehensive review of findings. Curr Psychiatry Rep, 2007. 9(6): p. 449-59")*
4) Assuming average length of MDD treatment cycles before process of elimination diagnosis as BDD
*5) Warden, D., et al., "The STAR*D Project results: a comprehensive review of findings. Curr Psychiatry Rep, 2007. 9(6): p. 449-59"*
6) DME machine learning model results
7) Shrestha, A., M. Roach, K. Joshi, J. J. Sheehan, P. Goutam, K. Everson, K. Heerlein and A. B. Jena (2020). "Incremental Health Care Burden of Treatment-Resistant Depression Among Commercial, Medicaid, and Medicare Payers." Psychiatr Serv 71(6): 593-601. "treatment resistance incurred higher annual costs (from $4,093 to $8,054 higher)" >> Assumed perfect treatment response =$8,054 USD savings converted to $10,463 CAD (2020$)
8) Russell, J. M., K. Hawkins, R. J. Ozminkowski, L. Orsini, W. H. Crown, S. Kennedy, S. Finkelstein, E. Berndt and A. J. Rush (2004). "The cost consequences of treatment-resistant depression." J Clin Psychiatry 65(3): 341-347. $11,024 USD in 2004$ average converted to 2020$ CAD
*9) Estimates based on results from the STAR*D study (reference 5 above). Assuming an average of 15.2 weeks until remission less 6 weeks for 1 treatment cycle before going on disability*
10) Expected improvement based on current ML model with limited dataset