Release Notes 2022-02-03 : : This is a letter for private circulation.

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Dear Recipients,

I'm having a hard time getting a hold of my mom's (Nancy Marchywka) current doctor, apparently Dr. Wilkens, and I had a similar problem contacting Dr. Lauren Atkinson. The issues here are a little difficult to discuss verbally anyway so I thought I would try to write up a few.

To get right to the point, I'm concerned her subjective non-specific complaints are due to real causes that may be easy to partially mitigate with a change in vitamins or medicines. These problems may have existed in more subtle forms for years leading to her poor outlook and DNR status. Hopefully, once mitigated her subjective experience will improve and remain self sustaining. Hypoperfusion (probably mesenteric, brain, and kidneys among others) ultimately related to nutritional problems and the presumed meningioma which speculatively may respond to diet are two important area for attention.

The following comments are based on my observation of her deteriorating physical and mental condition and the recurring diagnosis of "old age." Further, I understand the CT imaging has turned up a 1cm radio-dense object on the falx cerebri somewhere around the occipital or parietal lobe which apparently is assumed to be a meningioma. Her current medical therapy includes vitamin D and resperdal as well as blood pressure medicines Her mental condition is deteriorating to the point where physical therapy is difficult. While she is more confused than in prior years, her general attitude has not changed. Her recurring complaints of "not feeling good" or wanting to go to the hospital were initially easy to dismiss until eventually a UTI was discovered and treated. There was some hope she would recover a little after infection eradication but that has not occurred.

I understand the radio-dense lump is though to be asymptomatic in accordance with the medical literature I have skimmed although there may be some debate depending on details [20]. It is generally assumed to be slow growing especially when calcified although the relationship of size and mineralization to clinical symptoms remains unclear.

It is further my understanding that GI disturbances of various types are common in old age[3] but these too are often considered asymptomatic or undiagnosed.

Years earlier, I had hoped to get her onto a variety of nutritional supplements including amino acids, B-vitamins, and vitamin K. However, she has been quite reluctant to try these even as her overal condition deteriorated and she became more agitated and confused.

It seems reasonable to consider a neurological exam or otherwise evaluate the possibility of the radio-dense lesion contributing to her symptoms and having been maybe a more subtle factor in the past few years. Or for that matter find anything else that may have been missed.

However, in the meantime, I'm not sure the current medicines have the most favorable risk adjusted possible benefits profile. That is, the prognosis seems to be she will just keep getting older and that is that. However, the recent research literature suggests some fairly simple approaches that are compatible with existing treatment to varying degrees.

Since I will be elaborating a personal opinion with only passing literature references, I should document the basis for my opinions. I am neither a doctor nor a veterinarian but have spent a considerable amount of time optimizing vitamin supplements for a variety of dogs, including older ones, and creation of tools for documenting similar scientific efforts in informal settings. Prior to that, I had investigated biotech companies and explored related literature from a personal interest perspective. The more recent work has I documented with various online publications [10] [9] [8] [7] [7] [14] [12] [15] [13] [11] . During the decade or so of this interest, I have explored some open research topics or paradoxes that may be relevant to the present issue with my mother.

My thoughts are concisely stated below. Citations to my own works are generally documented with references to mainstream peer reviewed literature indexed on Pubmed. Other citations here are mostly Pubmed indexed but may be first-google-hits just to illustrate a point.

1. **get her off the Risperdal(risperidone)** The prescribing information outlines the concerns for elderly dementia patients with blood pressure problems [1]. It seems to knock her out with no obvious therapeutic or disease modifying role.

2. **avoid hypoperfusion** Most of the medicines attempt to decrease blood pressure but the concern is that the blood pressure may be required to achieve adequate perfusion or nutrient delivery (somewhere). Her recurring dehydration or hypovolemia can be temporarily fixed but that alone does not seem to create a sustained appetite or sense of well being.

3. **get her to try the amino acids, SMVT substrates, and B-vitamins generally** I outlined the case previously [8] explaining how various metrics of protein sufficiency don't help except in catastrophic situations and empirically things like dementia correlate with protein intake and have been observed to correct somewhat with amino acid supplements. I think my proposed solution will work at least as well as some published mixes as I also consider solubility issues. The neurotransmitter precursors are largely hydrophobic while lecithin and pantothenate solubility aids will be brain-beneficial too (see citations). Experience with the dogs here has been good. Chronic usage of amino acids in an old dog with slightly elevated ADMA proved beneficial [12]. Tryptophan in particular seems to be an important component of nutrient sensing [4] and its hydrophobicity may make it sensitive to digestive tract conditions.

4. **PCR urine and fecal samples** There is some possibility that her earlier repeat trips to the ER were due to false negative urine infection tests. PCR may help verify there are no undetected pathogens causing non-specific symptoms. If this is not medically warranted, I can send some to a research group for 16s rRNA PCR analysis as I do with dog samples. If you can do sterile urine collection, I have fecal sample tubes and prior experience with Zymo Research. [2]

5. **neurological exam or referal** I'm not sure what the problem is getting a neurological referral at this point although personally I would try the simple stuff (years ago). I understand she may not be a good candidate for surgery but other issues may come up on a better examination.

6. **add vitamin K to her vitamins along with B- vitamins including rotating SMVT substrates** There is a lot of evidence that vitamin D in isolation produces confusing results. While correlated with many diseases, as an intervention it is less effective [21] and it has possible deleterious effects. Deficiencies may correlate with vitamin K issues and the latter is may be a better intervention. Most recently, looking at the VITAL results [6] [5] small CVD and cancer benefits were found that did not reach significance although the adverse events are interesting [3] . Stones approached significance, GI bleeding and skin rash were significant in favor of vitamin D although nothing interesting in bruising. Stones you may suspect would be an issue with attempts to remove the vitamin D mobilized calcium although microbial involvement may be important. GI bleeding may relate to aspirin usage or relate to subtle vitamin K deficiencies. Either may suggest a prognostic imbalance which was undetected.

   Meanwhile, the role for vitamin K keeps expanding and in personal experience it has not created any risks for dogs with heartworm. One pregnant dog with heartworm and abdominal lumps (The vet said they were fibroids) did just fine with 10mg/day of vitamin K[16] supporting a proposed curve suggesting broad safety at high doses [15].

   Accumulating evidence presents a role for vitamin K in brain function and cognition[1]. Recently, a role for vitamin K along with vitamin D for sulfatide production has been observed [19]. Results remain confusing however.

   Calcium control may have general benefit but in particular with any ectopic or inappropriate mineralization such as that presumed in her brain.

   Some indication that protein S expression changes in meningioma [22] and there is some evidence of utility against cancers [23] and a relationship to ectopic calcium deposition [17] and osteoporosis [18]. One study suggests improvement for older women in fracture and cancer without changes in bone mineral density [2] making my point about quality rather than quantity (bone is not chalk and osteoclasts may simply be removing chalk).

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[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020272s085,020588s072,021444s058lbl.pdf
[2] https://files.zymoresearch.com/protocols/_r1100-50_r1100-250_r1200-25_r1100-125_dna_rna_shield.pdf
[3] https://www.nejm.org/doi/suppl/10.1056/NEJMoa1809944/suppl_file/nejmoa1809944_appendix.pdf

Can we find some way to explore any of this, determine it is not worthwhile, or find a better strategy? I was hoping to at least get her to try the amino acids but have not had much luck especially now that she is rejecting food.

If I had to pick one simple thing it would be the tryptophan mixed with both calcium pantothenate, which may help wet tryptophan, and a brain-useful emulsifier like lecithin. This is especially important if mixed with some drink like Ensure as it tends to float on the top without the solubility aids.

Thanks.

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Appendix A: Symbols, Abbreviations and Colloquialisms

TERM definition and meaning

Appendix B: Citing this work

Note: This is mostly manually entered and not assured to be error free.
This is tech report MJM-2022-006.

Version	Date	Comments
0.01	2022-02-02	Create from empty.tex template
-	February 3, 2022	version 1.0 MJM-2022-006
1.0	20xx-xx-xx	First revision for distribution

Released versions,
build script needs to include empty releases.tex

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Supporting files. Note that some dates,sizes, and md5's will change as this is rebuilt.

This really needs to include the data analysis code but right now it is auto generated picking up things from prior build in many cases

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