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A Clinical Program for Chronic Complex Disease:

Raising the Standard of Assessment and Care for People Living with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, Fibromyositis Syndrome and Related Conditions

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A Clinical Program for Chronic Complex Disease

Purpose: The purpose of this paper is to outline the rationale and design of a clinical program that will provide a model of assessment for people with a group of complex chronic diseases. Such a centre will provide leadership and work in partnership with the health care community to embrace best practices in state of the art management, and to leverage scientific infrastructure in BC to optimize the probability of identifying clearer causes.

Why Now?

Community groups have long identified that people living with some debilitating chronic complex diseases are having a hard time accessing a consistent standard of care in a coordinated fashion within the health care system. In September of 2010, the British Columbia Ministry of Health Services formally asked the Provincial Health Services Authority to consider what might be done to better serve patients with complex symptoms possibly related to underlying infectious disease and further, how the province could contribute to improved understanding of etiology.

In the same time frame, (August 2010), a paper was published which provided independent validation of an association between the Chronic Fatigue Syndrome and a family of murine retroviruses. These observations require further replication and closer study with respect to both validity and cause and effect.

In the past half decade, BC scientists have adopted a number of new methods which could allow the province to make a significant contribution to understanding in this field. Rapid development in the field of metagenomics has come from breakthroughs in genome sequencing and bioinformatics. This means that scientists can search not only for *organisms* that might play a key role, such as retroviruses or *Borrelia burgdorferii* (the Lyme agent), but can also gain better insight into the role of host factors such as immune expression. This approach has yet to be applied broadly in this field.

This paper outlines a plan to address a large unmet need for clinical assessment and support, and to fund a study to learn more about the cause of these syndromes.

Background

There are a variety of chronic complex diseases leading to disability in British Columbians where a cause is unknown, but where there is a high index of suspicion that an infectious pathogen may be playing a role. This section outlines some of the most prevalent recognized conditions in this category.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

ME/CFS is a debilitating disease of unknown etiology responsible for a large burden of illness in British Columbia and Canada(1). Canadian Community Health Survey data indicate that an estimated 38,000 British Columbians report a diagnosis of ME/CFS(2). Among Canadians with 23 chronic conditions, those who reported ME/CFS consistently ranked as having more unmet medical and homecare need, less food security, more marginalization, more need of help with tasks, greater difficulty in social situations, less ability to work and lower personal income.

ME/CFS typically follows an acute or sub-acute onset, often following a time-limited viral infection, leading to speculation about infectious disease as trigger or ongoing cause. Only 10% of adults experience full recovery. ME/CFS affects all races and socioeconomic groups(1).

While many people will experience fatigue at different points in life, ME/CFS is distinguished by the long duration of symptoms, a clear exacerbation with exertion, sleep dysfunction, accompanying pain (in the form of myalgia or headache) and the presence of other characteristic symptoms. The Canadian Consensus definition (see appendix 1) makes use of these characteristic symptoms to arrive at a reasonably specific diagnosis. Notably, it requires that certain other conditions of known etiology which could produce similar symptoms have been excluded.

Causes of ME/CFS

The cause of ME/CFS is unknown. Over the years there have been various working hypotheses implicating roles for viruses (EBV, HHV-6 or 7, Enteroviruses, etc.), Chlamydia, Mycoplasma, Borrelia, environmental triggers, immune dysregulation (especially of RNAse L) and mitochondrial dysfunction. (1;3)

Fibromyalgia Syndrome

Primary fibromyalgia is a common yet poorly understood syndrome characterized by diffuse chronic pain accompanied by other somatic symptoms, including poor sleep, fatigue, and stiffness, in the absence of disease. (4) Fibromyalgia does not have a known distinct cause or pathology. Accruing evidence shows that patients with fibromyalgia experience pain differently from the general population because of dysfunctional pain processing in the central nervous system. Aberrant pain processing, which can result in chronic pain and associated symptoms, may be the result of several interplaying mechanisms, including central sensitization, blunting of inhibitory pain pathways, alterations in neurotransmitters, and psychiatric comorbid conditions.

Lyme Disease

Lyme disease is a tick-transmitted infection caused by *Borrelia burgdorferi* (5).
The first sign of infection is usually an erythematous circular rash called erythema migrans (EM). The EM rash typically occurs 7-14 days after infection and when diagnosed on physical examination, even in absence of other Lyme-specific signs/symptoms or positive laboratory tests, establishes the diagnosis of Lyme disease (6). In contrast to erythema migrans, a localized tick-bite reaction occurs within hours of the bite, expands over hours (not days), and resolves within 48 hours.

Early Disseminated Lyme Disease

Untreated, the infection may spread over several weeks to months leading to three main syndromes:

- **Neurologic:** in about 5% of untreated patients neurological abnormalities such as aseptic meningitis and cranial neuritis may develop including Bell's palsy and radiculoneuritis. (7)

- **Musculoskeletal**: migratory joint and muscle pains without objective signs of swelling.

- **Cardiac**: although rare, cardiac manifestations can include atrioventricular block and acute myopericarditis. (7)

Late Disseminated Lyme Disease

Weeks to years after onset of infection (mean 6 months) episodes of swelling and pain in large joints (especially the knees) develop in up to 60% of untreated patients, leading to chronic arthritis. Some patients develop chronic axonal polyneuropathy or encephalopathy. Lyme disease is rarely, if ever fatal although patients with late disseminated disease can have severe, chronic and disabling symptoms (7;8).

'Chronic' Lyme Disease and Current Controversy

Most cases of Lyme disease are successfully treated with antibiotics. Treatment is most effective if begun early in the course of illness. However, a percentage of patients with Lyme disease may have lingering symptoms that last months to years, even after treatment with antibiotics. These symptoms include muscle and joint pains, arthritis, cognitive defects, sleep disturbance, or fatigue. The biological basis of the syndrome is not known (9). There is some evidence that it can result from an autoimmune response, in which a person's immune system continues to respond even after the infection has been cleared. There is no consensus that chronic *Borrelia burgdorferi* infection persists among such patients after receipt of recommended antibiotic treatment regimens. Despite anecdotal reports of benefit, antibiotic therapy has not been shown to be consistently useful in randomized controlled trials so that most medical guidelines do not recommend antibiotics for patients with chronic (≥6 months) symptoms after they have already received recommended treatment regimens for Lyme disease. Nevertheless, many patients who see no other therapeutic options will continue to seek this treatment. Long term antibiotic treatment for this and other conditions has been occasionally associated with severe adverse effects, including death (10;11).

In addition, there are a group of persons with symptoms such as fatigue, memory changes and musculoskeletal pain who have never had a history of acute Lyme disease and who have been identified by some physicians as suffering from chronic or late Lyme disease. The methods or tests used by these practitioners to arrive at a diagnosis have not been sanctioned or externally validated by testing authorities in North America and Europe.

However, what is clear is that while there is controversy about cause, this is another group of patients with considerable symptomatic overlap with ME/CFS who have unmet health care needs and a requirement for state of the art investigation and care.

Lyme Disease Diagnostic Testing in BC

Laboratory testing for Lyme disease largely relies on detection of antibodies in a person's blood. One source of confusion is that antibodies that react to *Borrelia burgdorferi* proteins can also be induced by infection with microbes other than *Borrelia burgdorferi* (12). Thus antibody tests can yield false positive results unless properly interpreted (13). The PHSA Public Health Laboratories recommends a two-step process to test for antibody evidence of Lyme disease in accord with recommendations by the American Public Health Laboratory Network, US Centers for Disease Control, Canadian Public Health Network and similar international authorities. Even after curative antibiotic treatment, antibodies may persist in the blood for years; therefore a positive antibody test post treatment is not considered indicative of treatment failure. (14).

The Murine Retrovirus Hypothesis – Could a Newly Identified Virus Cause ME/CFS?

In 2009, Lombardi and colleagues identified a strong association between the presence of a murine retrovirus (XMRV) and the Chronic Fatigue Syndrome. (15) The virus was found in 67% of patients compared with 3.7% of healthy controls. The strength of association was notable, so it was disappointing when 5 subsequent papers failed to identify the virus in similar studies. (16-20)

Just as the hypothesis seemed dead, Lo and Alter reported finding a murine retrovirus in 32 of 37 (86.5%) of ME/CFS subjects compared with only 3 of 44 (6.8%) healthy volunteer blood donors. (21) This paper differed from the previous in representing a broader phylogenetic inquiry and offered a possible explanation for the negative studies – the prior investigators had been looking for one specific virus when the relevant association might be with a family of viruses.

At this point, more work is needed to understand whether the observed relationships could be laboratory artifact or whether they are real. (22) If there is an association with murine retroviruses, there also needs to be more positive evidence of cause and effect. Finally, since the role of these viruses is not yet clear, any studies of causation in this population should be cognizant of other possible microbial and host elements.

The Issue of Complexity

“In cutting up a system (into its elements), the Analytic method destroys what it seeks to understand”(23).

There is considerable danger in oversimplifying plans for evaluation and management of these disorders. When underlying causes are not yet known and clear biological markers with high predictive value remain elusive, much relies on characterizing patients according to their symptoms. Symptoms cannot be experienced or measured by the clinician and must be understood from the point of view and context of the patient. While forming diagnoses and definitions out of groups of such symptoms may prove helpful for studies, there is a real risk of missing the importance of interactions between symptoms that will vary between individuals. Therefore, while a standardized approach to assessment may be desirable for some reasons, each person needs to be assessed individually.

The implications of complexity to clinical care are that individual assessment is needed at the same time as some degree of standardization. Clinicians and patients need to learn about the condition from each other.

The implications to research and discovery are that clinicians and scientists do not yet know all of the right questions - let alone the answers. Therefore, qualitative methods are required to generate fresh hypotheses. Qualitative methods refer to an array of techniques where patients themselves identify themes and hypotheses that may be relevant to their well-being. This could involve themes of cause, care, or of interaction with health care system or society. This is in contrast to standard quantitative science where we use experimental methods to answer questions we have already thought of ourselves. We use this iterative qualitative approach to increase the chance that we will be asking the right questions. In the following proposal, we seek to add to this approach by testing not only established hypotheses, but generating new ones through clinical interaction and the science of metagenomics.

It should be noted that while such complexity seems daunting, the challenges are not dissimilar from those of individual management of other chronic diseases, such as diabetes. Regular evaluation of symptoms over time allows an ongoing assessment of trends in well being and how these are correlating with interventions.

Reasons for Perception of Unsatisfactory Care by Patients

There are several factors that have led to poor satisfaction with care which must be considered when designing a clinical service for people with ME/CFS and related conditions.

1) These syndromes have no one clear unambiguous biological marker on which to hang a diagnosis. This can only be overcome by use of meticulous clinical assessment and case definitions in the short term, and a search for specific causes and markers in the longer term.

2) The average patient needs at least a 90 to 120 minute preliminary assessment, and follow-up visits may also need to be fairly lengthy. This creates very poor economic incentive for health care workers dependent on fee for service to make room in their practices.

3) Since causal pathways are not well understood, there is a risk of confusing a psychological consequence of an illness with its cause. Unfamiliarity with diagnostic criteria may lead to mislabeling (e.g. depression), referral elsewhere and a revolving door of specialist visits with no single care provider coordinating care.

4) Information on modalities that help people is not well codified and physicians feel that they can do nothing.

5) Some patients have a firm belief in a specific cause. This can impede the search for other remedial factors or lead to pressure for specific forms of therapy which the clinician feels are not evidence-based.

The Importance of Managing Hope and Client/Patient Expectations

Thousands of people with ME/CFS and related conditions have had a challenge obtaining a consistent standard of care to date. There will be great hope that a new initiative will immediately correct this deficit. It will be important to communicate clearly that we will build a strong working model and have plans to disseminate learning and standards or practice throughout the province, but that this cannot happen overnight.

Chronic Disease Management in British Columbia

British Columbia has a strong model of chronic disease management for arthritis, asthma, cardiac disorders, diabetes and chronic pain. Similar efforts are in place for known chronic infectious diseases such as HIV and viral hepatitis. The large unmet need for patients with ME/CFS, FMS and similar syndromes represents a challenge but also an opportunity to extend the province’s approach to chronic disease management and investigation.

Model for a Clinical Program

After consulting with caregivers and community, we are envisioning a clinical care program model in which staff contributes to improving the standard of practice throughout the province.

Most people consulted on clinical services for ME/CFS insisted on the need for a physical dedicated clinic. Virtual services for public and professional education could represent considerable added value, but proper assessment and testing can only be achieved in person.

Such a clinic could make use of space used for other purposes, but should be cognizant of the need for a clean, accessible, irritant-free environment and of a setting which is unlikely to lead to perceptions of stigmatization. There should be proximity to transit, accommodation and other relevant services. The optimal location for such a clinic would be in clinic space attached to a major teaching hospital.

A clinic should not be insular but needs to function as a designated focus of excellence in care of this patient group. This implies connectivity with other institutions and a capacity for continuing health education to improve the community standard of care. Evaluation and Referral Packages could be made available for download from the Web or completed online by patients / physicians. The suggested minimum workup could also be recommended per the website.

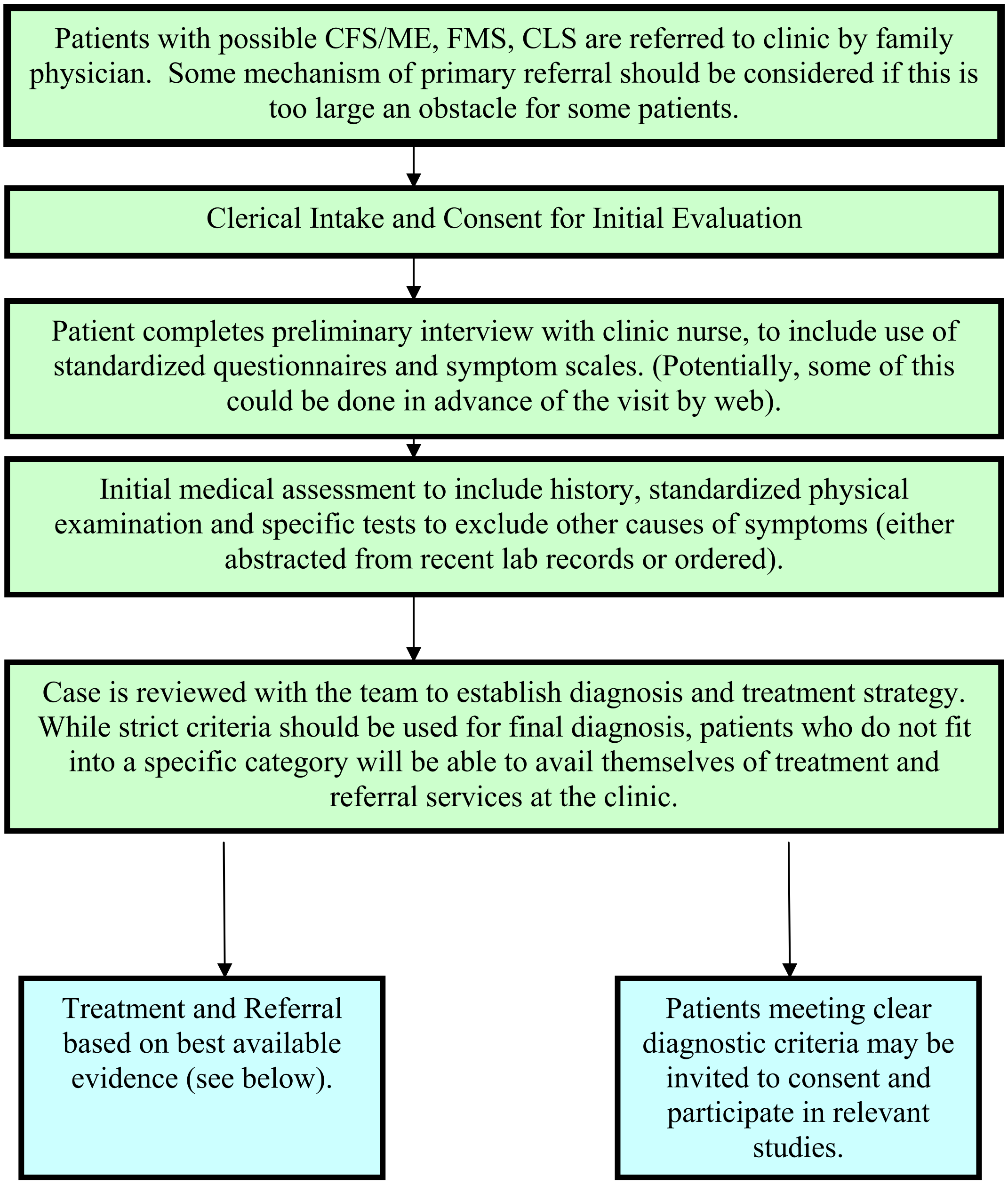
Conceptually, a clinic could be funded by BC's Provincial Health Services Authority. It is also important to consider the contribution of other health authorities, given their operation of the majority of clinic space and staff in the province. While BCCDC operates specific clinical prevention services for CD control, it is not the natural home for the ME/CFS service. This is because such a clinic needs to draw on the services of clinicians such as family practitioners, general internists and pediatricians and because the existing purpose-built clinic facilities for TB and STI management are not suitable for the patient population.

The recommended use of nurse practitioners or similar case workers within the clinic is essential. It provides ME/CFS patients with a model similar to what is seen in clinics for diabetes and other chronic diseases. It is respectful of the complex nature of ME/CFS and will assure that the clinic can provide sufficient time for all aspects of a proper assessment. Nursing functions include pre-interview, administration of various questionnaire scales, patient education, etc.

Advisory Board

We recommend that as with other services provided to a patient group that has endured some degree of marginalization in the past, an advisory structure is essential. This should most likely be comprised of two or three representative members of the affected community, and a similar number of medical/research experts chaired by the medical director.

Appendix One: Overview and Concept of Patient Flow



Patients with possible CFS/ME, FMS, CLS are referred to clinic by family physician. Some mechanism of primary referral should be considered if this is too large an obstacle for some patients.

Clerical Intake and Consent for Initial Evaluation

Patient completes preliminary interview with clinic nurse, to include use of standardized questionnaires and symptom scales. (Potentially, some of this could be done in advance of the visit by web).

Initial medical assessment to include history, standardized physical examination and specific tests to exclude other causes of symptoms (either abstracted from recent lab records or ordered).

Case is reviewed with the team to establish diagnosis and treatment strategy. While strict criteria should be used for final diagnosis, patients who do not fit into a specific category will be able to avail themselves of treatment and referral services at the clinic.

Treatment and Referral based on best available evidence (see below).

Patients meeting clear diagnostic criteria may be invited to consent and participate in relevant studies.

Appendix Two: Currently Relevant Screening Tests and Therapeutic Modalities

It is very important to identify any remediable causes of symptoms due to known causes. Much of this can be accomplished by a practiced and careful history and a physical examination with particular emphasis on complete neuromuscular and musculoskeletal examination. At a minimum, the following screening tests should be ordered or documented from recently performed tests done elsewhere:

- Complete Blood Count
- ESR
- Ca, P, Mg
- Glucose, electrolytes, Cr
- AST, ALT, ALP, GGT, Bilirubin
- TSH, CRP, ferritin
- RF, ANA, CK
- RPR, HIV, HBV and HCV serology
- Urinalysis
- Lyme Disease Serology

If there are positive findings on history, physical or laboratory tests, referral to one or more specialists for more complete assessment may be required. For example, any evidence of sensory, motor or reflex deficits may require neurological assessment to rule out other causes of neuromuscular disease.

Present-day Therapeutic Modalities

Modalities shown to be useful in this context include individualized counseling on exercise, activity and life-pacing, referral to a rehabilitation specialist with a focus of expertise in ME/CFS, stress reduction and relaxation, group discussion / education, nutritional advice and sleep maximization. (1) Pain management must also be included.

If a clinic is funded, further work will be required to review approaches with experienced clinicians from BC and elsewhere. For example, some informants mention that small group discussion and counseling on life-pacing can add value and may increase clinic efficiency.

Evidence-based treatments are to be preferred and clinicians should not be put in the position of being required to deliver therapeutic modalities where there is absence of efficacy and risk of harm to patients.

Appendix 3: Roles and Responsibilities within the Program

Medical Director

- Creates a standard of consistent, evidence-based assessment
- Monitors standard of care and stays current with evidence base for therapy
- Medical supervision of clinic staff
- Depending on skill-set – may provide research leadership or liaise with another study PI
- Time working for clinic should be supported by a salary structure or sessions
- Organizes his/her staff to provide outreach and continuing health education to other providers to assure an improving standard of care for ME/CFS patients in the broader community
- Liaises with hospitals, local public health units or community centres to extend awareness, information and support

Clinic Physicians

- Provide consistent initial assessments according to clinic guidelines
- Provide follow-up assessments as required
- Sessional or salaried compensation
- Must be skilled with pediatric as well as adult assessment
- Provide consultation services for referring physicians via Telehealth to determine if referral is appropriate

Nurse Practitioner / Case Management (Eventually 3 needed)

- Conduct much of the initial interview
- Conduct much of the standardized follow-up
- Conduct of group discussion education sessions
- To discuss relative time allocation of Nurse Practitioner vs MD
- Salaried

Clerical Support

- Patient intake
- Maintenance of charts
- Retrieval of lab tests

Web Master / Communications

- Maintaining an up to date website to support patient intake, professional education, public education and chat/blog functions
- Maintaining strong ties to affected community and coordinating meetings of advisory board
- Working with extramural funders to increase resourcing for studies or new modalities of care

- Planning formal course activities to disseminate best-practices among health care workers in British Columbia

Consultants that need to be available but need not be funded by the clinic

- Neurology
- Rheumatology
- Immunology
- Infectious Disease
- Medical Microbiology
- Psychiatry
- Psychology
- Rehabilitation Medicine
- Physiotherapy
- Nutrition
- Specialist in Sleep Disorders or referrals to Sleep Clinic
- Registered Massage Therapy
- Legal Advice
- Paediatrics

Clinic Design Phase

It is expected that the medical director and one or more nurse practitioners will need the support of a research assistant to pull together materials to create an optimal design for patient flow. Literature will require reviewing in more detail than was possible for this proposal. Approaches, forms, scales and therapeutic strategies in use in other successful clinics should be reviewed and clinic documentation designed. Ideally, this will be supported by IMIT so that there are mechanisms to convert forms into electronic records. This planning must also be cognizant *a priori* of the need to organize information in such a way as to be able to analyze data for quality control and research purposes.

Staff Training Phase

It must be recognized that there are very few physicians or nurses working with a current focus on these syndromes. Accordingly, any plan for setting up a clinic must include initial paid training and ongoing study by staff. We envision a planned one week orientation in which knowledge of the conditions is reviewed, staff may hear patient perspectives, a thorough familiarization with assessment and relevant scales is effected, and there is review of effective treatment modalities and referral patterns. Long term, staff would need to conduct a “rounds” function for educational update at least every two weeks.

Appendix Four: Study Considerations

An early goal of the clinic, once it has established a pattern of consistent patient assessment, will be to contribute to knowledge in this area.

Initially, we propose a modest case-control study in which patients with clear ME/CFS are compared with healthy controls, a chronic disease control group and, if funding allows, a group with FMS.

The objectives of this study would be to:

a) Formally test the hypothesis of an association between ME/CFS and murine retroviruses in ME/CFS patients in BC, and
b) To look for other microbial and host factors associated with ME/CFS (hypothesis generating approach)

In this study, groups of 25 ME/CFS, 25 FMS, 25 healthy controls and 25 controls with a known chronic disease (RA or MS) would be recruited. (This sample would be sufficient to test the hypothesis of a significant odds ratio exceeding 5 between CFS and control groups for murine retrovirus).

The two control groups (combined n=50) would need to be assessed using the standard clinic approach as used for patients referred to the clinic. This will generate costs for clinic personnel and laboratories. (See budget).

All subjects would have blood drawn for serum and peripheral blood mononuclear cells (PBMC).

The primary outcome variable would be detection of a NA sequence from PBMCs compatible with a murine retrovirus. This determination would take care to learn lessons from published papers: a broad inquiry of the gag gene would be used; there would be care to properly blind test and to use the same lots of reagents for testing of cases and controls.

Secondary outcome variables (or hypothesis-generating studies) would be:

a) Serology for organisms potentially associated with ME/CFS including Borrelia (C6 peptide), Anaplasma, Ehrlichia, Babesia, Ricketsia, Q fever, Bartonella, Francisella, Mycoplasma, and spiroplasma.
b) Metagenomic analysis of nucleic acid derived from the PBMC pool to search for differences between cases and controls with respect to microbial nucleic acid, as well as host nucleic acid and transcription. This technique has enormous power to identify factors associated with disease that have not been identified using other methods.
c) Consideration of use of an oligopeptide array (McGeer) to examine cross reactivity between XMRV and other murine retroviruses in order to resolve contradictory studies in the literature.

Lyme positive controls should be included to assess sensitivity of the various methods. Specimens will be sought from 2 patients with culture positive late Lyme arthritis and 2 patients with culture positive Lyme neuroborreliosis.

Analysis

The principle analysis would be assessment of the unadjusted OR for murine retroviruses.

Other differences will be evaluated as secondary analyses using crude odds ratios and an adjusted level of significance.

Role of PI

Responsibility for all aspects of conduct of the study:

- Consults with experts and community
- Finalizes protocols for study
- Assures compliance with ethical standards and full consent
- Manages budgets and assures proper use of funds
- Keeps current with relevant literature to avoid duplication of studies done elsewhere
- Supervision of study staff
- Regular meetings with clinic staff

Appendix Five: People Consulted in the Development of this Proposal

- Bruce Carruthers, Internist and Specialist in ME/CFS Care (Semi-retired)
- Jan Venter, Family Physician and Practicing Specialist in ME/CFS
- Sherri Todd, National ME/CFS Action Network (BC Chapter)
- Margaret Parlor, National ME/CFS Action Network
- Sue Drake Johnson, Affected Community Representative
- Kathleen Ferns, Affected Community Representative
- Bill Bowie, Infectious Diseases
- Bonnie Henry, BCCDC
- Patrick Tang, PHSA Labs
- Judy Isaac-Renton, PHSA Labs
- Jennifer Gardy, BCCDC
- Bob Brunham, BCCDC
- Muhammad Morshed, BCCDC
- Tom Perry, Department of Medicine, UBC
- Andy Mason, Department of Medicine, University of Alberta
- Ted Steiner, Infectious Diseases

Appendix 6: Canadian Clinical Working Case Definition for ME/CFS

Patients must have:

1. Fatigue
2. Specifically also Post-exertional malaise or fatigue
3. Sleep dysfunction
4. Pain (usually myalgias or HA)
5. Two or more of a list of neuro-cognitive manifestations
6. At least one symptom from two of the following categories: Autonomic (e.g. bowel/bladder, tachycardia, postural hypotension); Neuroendocrine (temperature disturbance, marked weight/appetite change, etc.); Immune (LAN, sore throat, malaise, new "sensitivities" to foods, allergens, etc.)
7. Duration of illness at least 6 months

Diagnosis also requires systematic exclusion of various endocrine, rheumatologic and neurological causes of similar symptoms.

Budget Considerations

Clinic:

Assumptions: 2 physicians, 2 nurses, small start up seeing maximum 5-6 patients per day 5 day workweek, 7 hours of contact time per day
Assumes that clinic, and setup (computers, etc) are provided using existing resources and space

Item		One time cost
Initial website development, creation and hosting, using Content Management System for ease of maintenance and further development	Software, development time and webmaster, functionality development and refinements	**$65,000**

Item		Annual Cost
Medical Director	0.5 FTE	$125,000
Physician Sessions(specialist)	535 specialist sessions (at 478.66cost) 50 weeks, 5 days a week, 535 sessions per year, and assuming a 3% increase in 2011	$295,800
Alternate salaried Family physician (1 of each at quoted initial workup would be able to see only 2 per session, 4 per day).	535 FP sessions at 405.78 per session. 535 sessions and assuming 3% increase in 2011	$252,350
Nurse Case Manager or Nurse practitioner	2 position w. Nurse practitioner 92k per yr plus benefits **OR** Senior Nurse: 85k/yr including benefits	$210,000
Clerical	1 receptionist, 1 transcriptionist including benefits	$84,000
Screening Lab Tests	For patients – MSP cover *	
	For 25 controls – 15 tests at MSP rate	$12,000

Webmaster/communications resources for online presence and ongoing updating	.4 webmaster for ongoing updates 1	$26,000
Supplies-office		$5,000
Supplies- clinic		$25,000
Total assuming space and IT support provided		**$1,074,150**

* We estimate net savings to MSP over time with respect to screening tests because coordinated care at one centre and clear listing of tests of known value will lead to reduced overall billings to labs as redundant testing by various practitioners and testing of dubious value can be eliminated.

In the event that a higher volume of patients would be seen, the increase might be seen only in the sessional hours, as the nursing and clerical support would be able to support a significant increase.

Study

Item		Cost for Full Study
PI	10%	$ 24,000
Research Nurse	85,000 x 2 years	$170,000
Research Epidemiologist	50,000 half time x 2 years	$100,000
Lab testing PCR	$50 per 3 tests x 100 study samples	$5,000
Indexing of Metagenomic Samples	6,000	$6,000
Sequencing of samples Bioinformatic Analsyis	50,000 35,000	$50,000 $35,000
Lab testing serology	15/test X 10 agents/subject x 100 subjects	$15,000
Genomics lab equipment lease	$11,000/mo x 1 yr	$132,000
Lab tech	1 FTE x 1 year	$70,000
Lab coordinator	0.25 FTE x 1 yr	$25,000
Controls and cost	100 people at 160 per participant	$16,000 honoraria if required
Research oversight committee	4 meetings (includes travel, meeting costs, etc.)	$10,000
Dissemination	Publication costs, conference fees and travel for dissemination.	$10,000
Total		**$668,010**

Reference List

1. Carruthers BM. Definitions and aetiology of myalgic encephalomyelitis: how the Canadian consensus clinical definition of myalgic encephalomyelitis works. J.Clin.Pathol. 2007;60(2):117-9.

2. Parlor, M. Quest - Profile and Impact of 23 Chronic Conditions in the 2005 Canadian Community Health Survey. Profile and Impact of 23 Chronic Conditions in the 2005 Canadian Community Health Survey. (Communication #80), 1-16. 2009. National ME/FM Action Network.

3. Afari N, Buchwald D. Chronic fatigue syndrome: a review. Am.J.Psychiatry 2003;160(2):221-36.

4. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of fibromyalgia. Ann.Intern.Med. 2007;146(10):726-34.

5. Bratton RL, Whiteside JW Hovan MJ Engle RL Edwards FD. Diagnosis and treatment of Lyme disease. Mayo Clinic Proceedings 83(5), 566-571. 2008.

6. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America.[see comment][erratum appears in Clin Infect Dis. 2007 Oct 1;45(7):941]. Clinical Infectious Diseases.43(9):1089-134, 2006.

7. Control of Communicable Diseases Manual. 19th Editioned. American Public Health Association; 2008.

8. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin.Infect.Dis. 2006;43(9):1089-134.

9. Feder HM, Jr., Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP et al. A critical appraisal of "chronic Lyme disease". N.Engl.J.Med. 2007;357(14):1422-30.

10. Patel R, Grogg KL, Edwards WD, Wright AJ, Schwenk NM. Death from inappropriate therapy for Lyme disease. Clin.Infect.Dis. 2000;31(4):1107-9.

11. Holzbauer SM, Kemperman MM, Lynfield R. Death due to community-associated Clostridium difficile in a woman receiving prolonged antibiotic therapy for suspected lyme disease. Clin.Infect.Dis. 2010;51(3):369-70.

12. Johnson BJ, Robbins KE, Bailey RE, Cao BL, Sviat SL, Craven RB et al. Serodiagnosis of Lyme disease: accuracy of a two-step approach using a flagella-based ELISA and immunoblotting. J.Infect.Dis. 1996;174(2):346-53.

13. Notice to Readers: Caution Regarding Testing for Lyme Disease. Morbidity and Mortality Weekly Report 2005;54(5):125.

14. Gerber MA, Shapiro ED, Burke GS, Parcells VJ, Bell GL. Lyme disease in children in southeastern Connecticut. Pediatric Lyme Disease Study Group.[see comment]. New England Journal of Medicine.335(17):1270-4, 1996.

15. Lombardi VC, Ruscetti FW, Das GJ, Pfost MA, Hagen KS, Peterson DL et al. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. Science 2009;326(5952):585-9.

16. Erlwein O, Kaye S, McClure MO, Weber J, Wills G, Collier D et al. Failure to detect the novel retrovirus XMRV in chronic fatigue syndrome. PLoS.One. 2010;5(1):e8519.

17. Hong P, Li J, Li Y. Failure to detect xenotropic murine leukaemia virus-related virus in Chinese patients with chronic fatigue syndrome. Virol.J. 2010;7(1):224.

18. Jeziorski E, Foulongne V, Ludwig C, Louhaem D, Chiocchia G, Segondy M et al. No evidence for XMRV association in pediatric idiopathic diseases in France. Retrovirology. 2010;7:63.

19. Switzer WM, Jia H, Hohn O, Zheng H, Tang S, Shankar A et al. Absence of evidence of xenotropic murine leukemia virus-related virus infection in persons with chronic fatigue syndrome and healthy controls in the United States. Retrovirology. 2010;7:57.

20. van Kuppeveld FJ, de Jong AS, Lanke KH, Verhaegh GW, Melchers WJ, Swanink CM et al. Prevalence of xenotropic murine leukaemia virus-related virus in patients with chronic fatigue syndrome in the Netherlands: retrospective analysis of samples from an established cohort. BMJ 2010;340:c1018.

21. Lo SC, Pripuzova N, Li B, Komaroff AL, Hung GC, Wang R et al. Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors. Proc.Natl.Acad.Sci.U.S.A 2010;107(36):15874-9.

22. Weiss RA. A cautionary tale of virus and disease. BMC.Biol. 2010;8:124.

23. Cilliers, P. Complexity and postmodernism: Understanding complex systems. 1998. New York, Routledge.