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Ethics in Prion Disease

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Abstract

This paper is intended to discuss some of the scientific and ethical issues that are created by increased research efforts towards earlier diagnosis, as well as to treatment of, human prion diseases (and related dementias), including the resulting consequences for individuals, their families, and society. Most patients with prion disease currently are diagnosed when they are about 2/3 of the way through their disease course (Geschwind, Kuo et al. 2010; Paterson, Torres-Chae et al. 2012), when the disease has progressed so far that even treatments that stop the disease process would probably have little benefit. Although there are currently no treatments available for prion diseases, we and others have realized that we must diagnose patients earlier and with greater accuracy so that future treatments have hope of success. As approximately 15% of prion diseases have a autosomal dominant genetic etiology, this further adds to the complexity of ethical issues, particularly regarding when to conduct genetic testing, release of genetic results, and when or if to implement experimental therapies. Human prion diseases are both infectious and transmissible; great care is required to balance the needs of the family and individual with both public health needs and strained hospital budgets. It is essential to proactively examine and address the ethical issues involved, as well as to define and in turn provide best standards of care.

Keywords

Creutzfeldt-Jakob Disease; CJD; Prion disease; Ethics; Neurodegenerative disorders; Prion; Rapid dementia; Genetic prion disease; GSS; FFI; gPrD; Transmissible Spongiform Encephalopathies

1. Background on Prion Diseases

This paper discusses some of the scientific and ethical issues that are created by increased research efforts towards earlier diagnosis and treatment of human prion diseases (and related dementias), including the resulting consequences for individuals, their families, and society. In an era in which we are likely to find a treatment to halt, and possibly reverse, these devastating uniformly fatal illnesses, it is essential to proactively examine and address certain current and potential ethical issues.

1.1 What are prion diseases?

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are a group of rapidly progressive neurodegenerative diseases that occur when an endogenous protein, PrP^C (Prion related protein; C refers to the normal cellular form of the protein), transforms into an abnormal conformation, PrP^{Sc} (Sc stands for Scrapie, the prion disease of sheep and goats)

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(Prusiner 1982). This abnormally shaped protein is called the prion (pree-ahn). It is believed that prions promote this same abnormal conformational change in adjacent normal shaped prion proteins (PrP^C → PrP^{Sc}) that come in contact with prions. Once the process begins, the transformation of prion proteins into prions is thought to occur in an exponential manner, leading to the accumulation of prions. Some researchers believe it the accumulation of prions that leads to nerve cell injury and death (Prusiner 1998), whereas others believe that it is the transformation of PrP^C into PrP^{Sc}, or an intermediate, that leads to neurodegenerative disease (Mallucci, White et al. 2007).

For years many scientists thought scrapie, Kuru, CJD and related transmissible spongiform encephalopathies (TSEs) were due to “slow viruses,” in part because of their transmissibility and the prolonged incubation period between exposure and symptom onset (Gajdusek 1977; Prusiner 1998). It was discovered that the infectious agent could not be inactivated using methods that inactivate viruses and other microorganisms (Pattison 1965; Pattison 1965; Griffith 1967; Pattison and Jones 1967). Tikvah Alper, Ian Pattison and others postulated that the “scrapie agent” did not contain nucleic acid and first postulated it might be a protein (Alper, Haig et al. 1966; Alper, Cramp et al. 1967; Griffith 1967; Kimberlin and Hunter 1967; Pattison and Jones 1967). Several investigators showed transmission of the TSE causative agent from animal to animal could be prevented by treating the tissue using methods that destroy and denature proteins (Prusiner 1982). Stanley Prusiner confirmed the “scrapie agent” was a protein, isolated it, and named it a “proteinaceous infectious particle,” or prion (Prusiner 1982), receiving a Nobel Prize for his work in 1997 (Prusiner 1998). The prion hypothesis is further supported by the identification of the gene encoding PrP in humans, *PRNP* (Oesch, Westaway et al. 1985; Hsiao, Baker et al. 1989; Hsiao, Scott et al. 1990), and of mutations in this gene among patients with familial prion diseases (Goldgaber, Goldfarb et al. 1989; Hsiao, Baker et al. 1989). Prion diseases occur in humans and animals, and animal models have helped to show that the prion protein is sufficient and necessary to cause prion disease (Bueler, Aguzzi et al. 1993; Weissmann and Flechsig 2003; Watts, Balachandran et al. 2006). Over the past few years, the prion only hypothesis (that prions alone are necessary and sufficient to cause prion disease/TSEs) has been essentially proven through the creation of artificial prions *in vitro* which can cause prion disease (Legname, Baskakov et al. 2004; Barria, Mukherjee et al. 2009; Jackson, Borkowski et al. 2009; Sigurdson, Nilsson et al. 2009; Kim, Cali et al. 2010; Makarava, Kovacs et al. 2010; Soto 2011).

1.2 Human Prion Disease

Prion diseases are unique in medicine in that they can occur in three separate ways, sporadic, acquired and genetic (Watts, Balachandran et al. 2006). Sporadic Jakob-Creutzfeldt disease (sCJD) is thought to occur spontaneously and accounts for approximately 85% of all cases of human prion disease. Genetic prion diseases are caused by a mutation in the gene that encodes the prion protein, *PRNP*. They comprise about 15% of human prion disease cases. Though less than 1% of all prion disease is acquired, they are certainly the most well-known, in part due to the outbreak of Bovine Spongiform Encephalopathy (BSE) in the UK in the mid-1990s and the Kuru epidemic in Papua New Guinea in the early 20th century (Prusiner 1998).

1.2.1 sCJD—This article uses CJD to refer to all human prion diseases and sCJD to refer to sporadic CJD (though elsewhere in the literature sporadic CJD is sometimes referred to simply by the term CJD). Sporadic CJD typically occurs in one's late 60s, however there is a very wide range from early teens to 90s. These very young and very old cases are exceptionally uncommon (Brown, Cathala et al. 1986; Will 2004), with most patients falling ill in their 50s to 70s. It is typically a very rapid disease with a reported median survival of

about 4 months and a reported mean of 5–8 months; 85%–90% of all patients with sCJD survive one year or less (Brown, Gibbs et al. 1994; Pocchiari, Puopolo et al. 2004; Collins, Sanchez-Juan et al. 2006), although some patients survive for a year and a half or longer (Parchi, Giese et al. 1999). Toward the end of the disease course patients are usually in an akinetic-mute state (WHO 1998), and a majority of patients with CJD die from aspiration pneumonia.

1.2.2 gPrD—There are more than 40 known or suspected mutations in *PRNP* that cause genetic prion disease (gPrD), with new mutations being identified regularly (Mead 2006). These mutations are believed to increase the likelihood of the prion protein (PrP) changing shape into the prion, PrP^{Sc} (Prusiner 1998; Will, Alperovitch et al. 1998; Kong, Surewicz et al. 2004). Some genetic mutations cause human prion diseases that present almost identically to sCJD, with similar clinical features, time course, MRI, and EEG findings. Other mutations present with a more prolonged course, often years, with symptoms including slowly progressive ataxia, behavioral changes, cognitive impairment, and parkinsonism (Geschwind and Legname 2008). For a thorough review of clinical course as well as CSF, MRI and EEG findings by mutation, see the extremely informative chapter by Kong et al (Mitchell and Malladi 2010), or a paper on human genetic prion diseases by Simon Mead (Mead 2006). Quite notably, more than 60% of genetic prion disease cases have no known history of CJD in their family. There is often, however, a history of potentially misdiagnosed Alzheimer's, Parkinson's, or other movement or dementia related disorder (Will, Alperovitch et al. 1998; Kovacs, Puopolo et al. 2005).

Genetic prion diseases historically have been divided into three categories: familial CJD (fCJD), Gerstmann-Sträussler-Scheinker (GSS), or the exceedingly rare Fatal Familial Insomnia (FFI) (Brown and Mastrianni 2010). More than 20 point mutations have been associated with fCJD, including insertion mutations, and octapeptide insertions (OPRI). The most common form of fCJD, and any gPrD, is due to the E200K mutation. The majority of mutations causing fCJD usually present quite similarly to sCJD both clinically and in MRI and EEG findings. At least 15 *PRNP* mutations cause GSS, including point mutations, such as P102L, A117V, F198S, and others, as well as insertion mutations. There is a region in the prion gene between amino acids 50 and 90, in which there are octapeptide repeats (of 24 base pairs). In this region, octapeptide repeat insertion mutations sometimes occur. It is often stated that OPRI mutations with more than four 24 base pair repeats (OPRI) tend to present as GSS, whereas mutations with four or fewer 24 base-pair repeats typically present as fCJD, although this does not always hold true (Brown and Mastrianni 2010). GSS generally has a slower course than other prion diseases, with an average duration of about 5 years, depending on the mutation. Less commonly, patients with GSS can have a shorter disease course mimicking sCJD. Fatal Familial Insomnia (FFI) is caused by a single point mutation, D178N (with the cis codon 129 being methionine) and typically begins with severe, progressive insomnia and autonomic dysfunction. Cognitive and motor symptoms tend to appear later in the course of the disease (Lugaresi, Tobler et al. 1998).

It is generally considered sufficient for an individual to have a known causative *PRNP* mutation in combination with symptoms consistent with a gPrD to make a definitive diagnosis of gPrD. Testing for *PRNP* mutations, after genetic counseling, should be provided to all suspected CJD patients, as many forms of gPrD cases present similarly clinically to sCJD and might not have a positive family history (Kovacs, Puopolo et al. 2005). Furthermore, there is often significant neuropathological overlap between certain forms of fCJD and sCJD; neuropathology alone cannot distinguish them (Kong, Surewicz et al. 2004).

1.2.3 Acquired CJD—Acquired cases of CJD are exceedingly rare, but occur because prions are both infections and transmissible. These types of CJD, especially variant CJD (vCJD), currently are the most widely known to the public, due in large part to media attention surrounding an outbreak of vCJD in Europe that began in the U.K. in 1995 (Will, Ironside et al. 1996), peaking in the early 2000s. Although prion diseases are transmissible, they are not considered contagious, as it is difficult to transfer the disease from person to person. Transmission requires transfer of bodily tissue or fluids, usually directly from the nervous system, containing high levels of prions from one person to another (Will 2003; Brown, Brandel et al. 2006). The precise number of prions necessary for disease transmission varies depending on the type of prion disease, the strain of prion, and routes of inoculation. Direct intracerebral inoculation is the most efficient method of transmission. How to define whether a very low dose of prions is transmissible or infectious is difficult, as the animal being used might die during their normal lifespan before infection takes place (Dickinson, Fraser et al. 1975; McLean and Bostock 2000). Most titration experiments make dilutions based on the ID₅₀, which is the amount of inocula of prion containing material required to make 50% of the animals sick (McLean and Bostock 2000). As even dilutions of 1000 fold of the ID₅₀ still result in some transmission and the infeasibility of the number of mice required to do further dilutions, some feel that there is no safe dose of prions (Fryer and McLean 2011).

1.2.3.1 Kuru: Kuru appeared among the Fore tribes in Papua New Guinea at the beginning of the twentieth century. In the 1950's, Gajdusek believed Kuru to be a genetic disease, and undertook a major study of the disease and afflicted individuals in the area (Gajdusek and Zigas 1957). Kuru's transmissibility was shown via inoculation of affected human tissues into chimpanzee brains (Gajdusek, Gibbs et al. 1966). It was later demonstrated that this disease was spread through endocannibalism. Although this practice subsided in the latter half of the twentieth century, cases have been reported more than 50 years after the practice of endocannibalism was stopped by missionaries, suggesting possibly very long incubation periods. This disease is now essentially extinct (Collinge, Whitfield et al. 2006).

1.2.3.2 vCJD: A new form of human prion disease was discovered in the UK in 1995. To date, more than 200 cases of vCJD have been identified, primarily in the UK and to a lesser degree in France and mostly other European countries (UK National CJD Surveillance Unit 2012). Variant CJD has been linked to the consumption of cattle affected with bovine spongiform encephalopathy (BSE; also called Mad Cow disease), a prion disease. It is believed that BSE occurred in cattle due to the feeding of sheep parts inadvertently contaminated with scrapie, a prion disease of sheep and goats (Will, Ironside et al. 1996; Bruce, Will et al. 1997; Scott, Will et al. 1999). Although some clinical features of vCJD overlap with those of sCJD, these diseases differ in several ways. The majority of vCJD patients are quite young compared to other human prion diseases. The median age of onset is 26 and death is 28, but the age range of onset is 12 to 74, with a median duration of 14 months (mean 16 months)(Corato, Cereda et al. 2006; Heath, Cooper et al. 2011). The first symptom is typically psychiatric, most often depression anxiety, apathy, withdrawal, and/or delusions followed by development of a movement disorder, cognitive impairment and sometimes painful dysesthesias (Zeidler, Johnstone et al. 1997; UK National CJD Surveillance Unit 2008; Heath, Cooper et al. 2011). When patients come to medical attention, only about 18% of cases are thought initially to have a neurologic etiology; most are presumed to be psychiatric in origin (Heath, Cooper et al. 2011). Much like in other forms of human prion disease, patients with vCJD have progressive cognitive impairment and are usually in an akinetic mute state by the end of their disease process and succumb to aspiration pneumonia (Will, Zeidler et al. 2000). Clinical diagnosis is made based on the constellation of symptoms, specific hyperintensities on brain MRI (Zeidler, Collie et al.

2001) and tonsil biopsy in some cases (Hill, Butterworth et al. 1999; Will, Zeidler et al. 2000; Heath, Cooper et al. 2011). Unlike other forms of human prion disease, in vCJD prions are found in high concentrations outside the central nervous system in the lymphoreticular system (Hill, Butterworth et al. 1999). Although this has the advantage of allowing for premortem pathological diagnosis via tonsillar biopsy, it also increases the risk of iatrogenic transmission. Variant CJD is the only human prion disease definitely known to be transmitted by transfusion of blood products (Health Protection Agency 2007; Peden, McCardle et al. 2010). Also unique to vCJD and Kuru are the presence of a high concentration of amyloid florid plaques in the cerebellum and cerebrum (Will, Ironside et al. 1996). Tests to detect vCJD in the blood are under development (Cooper, Andrews et al. 2013) and at least one test has shown 100% specificity, but only 71% sensitivity (Edgeworth, Farmer et al. 2011).

1.2.3.3 iCJD: In 1974, the first case of likely iatrogenic transmission of CJD, via corneal transplant, was published (Duffy, Wolf et al. 1974). Since then, several other routes of transmission to humans, including human pituitary hormones (Gibbs, Joy et al. 1985; Koch, Berg et al. 1985; Powell-Jackson, Weller et al. 1985) and dura mater grafts (Martinez-Lage, Poza et al. 1994; Centers for Disease Control and Prevention (CDC) 1997; Meissner, Kallenberg et al. 2009; Yamada, Noguchi-Shinohara et al. 2009) as well as through contaminated neurosurgical instruments have been identified (Gibbs, Asher et al. 1994). Standard sterilization techniques used for hospital equipment are not adequate to inactivate prions (Bellinger-Kawahara, Cleaver et al. 1987; Bellinger-Kawahara, Diener et al. 1987; Peretz, Supattapone et al. 2006). Special precautions are recommended when performing any procedures involving direct contact with central nervous system tissue (e.g., neurosurgery) to avoid unnecessary exposure to infectious agents (FDA 2010). Due to the difficulties associated with sterilizing prions, as well as the high likelihood that patients with prion diseases receive misdiagnoses prior to correct diagnosis (Paterson, Torres-Chae et al. 2012), there have been more than 400 cases of iatrogenic CJD (iCJD) from the use of dura mater grafts, corneal transplants, human pituitary hormones derived from cadavers, blood transfusions, and neurosurgical equipment including sterilized and reused EEG depth electrodes (Brown, Preece et al. 2000; Will 2003; Brown, Brandel et al. 2006). The majority of human growth hormone and gonadotropin related cases of iCJD took place in Australia, France, and the United States, and measures have since been implemented to prevent further transmission via these routes (Brown, Brandel et al. 2006). There continue to be, however, cases of potential iCJD transmission despite current World Health Organization recommendations (Brown, Brandel et al. 2006; WHO 2006).

Though according to the Centers for Disease Control (CDC) no suspected cases of transmission of CJD from surgical equipment have been reported since 1976 (CDC 2010), there have been several cases of potential exposure with as of yet unknown outcomes. On September 10th, 2004, a patient at Emory University hospital not initially suspected of having prion disease prior to brain biopsy was later diagnosed with CJD. Before the diagnosis was made, the neurosurgical equipment used in the procedure was mixed with surgical equipment used in other patients and not treated in a way as to decontaminate prions. This equipment was then used on additional patients before the initial case was correctly diagnosed as CJD. None of this equipment was treated with methods used to reduce prions. Ninety-eight brain and spine surgery patients might have been exposed to prions, all of whom were contacted by the university and told of their risk. The University Hospital also published press releases on October 1st and October 12th of that same year notifying the general public of the potential risk, outlining the steps they were taking to prevent contamination, and confirming the original patient's diagnosis (Emory University 2004)(Associated Press 2004).

As recently as July 2012, Greenville Hospital System in South Carolina performed a surgical brain procedure on an individual who was later diagnosed with CJD. Though all tools used in this surgery were sterilized according to rigorous U.S. protocols to reduce contamination from viruses or bacteria, they were not treated with methods to decontaminate against prions. Apparently, 11 patients who had brain surgery were later notified that they may have been exposed to prions through their surgeries (Diller 2012). At UCSF, in which probably the highest number of patients with prion disease are evaluated clinically in the United States, even procedures with exposure to less risky materials, such as CSF (WHO 2006), are performed with special CJD precautions; although the risk likely is quite low, UCSF has been conservative and erred on the side of caution due to the high volume of CJD patients seen (UCSF Medical Center 2012).

1.3 Animal Prion Diseases

Prion diseases are found in a variety of animals, including Scrapie in sheep and goat, BSE in cattle, chronic wasting disease (CWD) in deer, elk and moose. Interspecies transmissibility has been shown through a variety of methods, most notably from cattle to humans via ingestion of BSE-contaminated beef. Animal models in the laboratory, such as mice (particularly when genetically modified to carry the human prion gene), bank voles, and chimpanzees, have been quite successful in demonstrating potential interspecies transmissibility (Watts, Balachandran et al. 2006).

1.3.1 Scrapie—Scrapie has been seen among sheep flocks in Europe for more than 250 years. Through these flocks, the disease spread to other parts of the world (Dickinson, Fraser et al. 1975; Luhken, Buschmann et al. 2007). Affected sheep and goats often develop severe itching and “scrape” their skin against fences or trees, hence the name Scrapie.

1.3.2 BSE—Bovine Spongiform Encephalopathy (BSE) is a prion disease of cattle. It is estimated that the first infections of BSE occurred in the 1970s; two cases were identified in 1986. It is believed that these cases originated from scrapie-infected meat and bone meal. Most evidence suggests cattle from the U.K. contracted BSE from being fed animal feed containing of scrapie-infected sheep, which would be a further indication of prions' ability to cross species barriers (Wilesmith, Wells et al. 1988; Wilesmith, Ryan et al. 1991; Bradley and Wilesmith 1993; Hope, Wood et al. 1999). There is a strong link between consumption of BSE infected beef and vCJD via both epidemiologic and laboratory data (CDC; Bruce, Will et al. 1997; Hope, Wood et al. 1999; Scott, Will et al. 1999). Though there have been significantly stricter regulations on cattle feed and on testing for BSE within cattle herds, there continue to be cases of BSE in several countries each year (World Organization for Animal Health (OIE) 2013; World Organization for Animal Health (OIE) 2013).

1.3.3 CWD—Chronic Wasting Disease (CWD) is a prion disease of white-tailed and mule deer, elk and moose in the United States. CWD has been found in captive and wild ranging animals (Williams 2005; Baeten, Powers et al. 2007). This is important because though it might be feasible to eradicate prion disease in captive herds, complete elimination of prion diseases in wild herds would be very difficult. Prions are found in large concentrations in affected deer, moose and elk in lymphoid as well as central nervous system tissue (Williams 2005). CWD prions might also be shed from feces and bodily fluids such as urine and saliva, indicating another possible route of transmission (Safar, Lessard et al. 2008; Haley, Seelig et al. 2009). CWD has been shown to be transmissible to other species via intracerebral inoculation, and laboratory studies suggest CWD might be transmitted orally (Safar, Lessard et al. 2008). No studies have yet shown that CWD is transmissible to humans (Sandberg, Al-Doujaily et al. 2010; Wilson, Plinston et al. 2012). Significant portions of the population in areas with deer and elk infected with CJD hunt these animals for meat. Though hunters are

advised to not interact with animals that appear sick, wear rubber gloves when dressing and processing animals, and avoid handling or consuming brain and spinal tissues, in practice it has been difficult to have hunters follow recommendations that are based solely on a theoretical risk (Zimmer 2011).

1.4 Epidemiology

The annual incidence of human prion diseases worldwide is about 1–1.5 per million cases per year with some variability between countries and from year to year (Parchi, Strammiello et al. 2009; Andrews 2010; Holman, Belay et al. 2010). This translates to between 250–400 in the United States and about 6000 new cases worldwide per year (Brown, Cathala et al. 1986; Ladogana, Puopolo et al. 2005). Some countries, including Switzerland, seem to have a slightly higher incidence of human prion disease, around 1.9 per million per year (Ladogana, Puopolo et al. 2005), but this is might be due to ascertainment bias; it is easier to track all cases in small, highly developed countries. Most forms of CJD tend to occur in patients of a rather narrow age range (50s–70s with peak around age 68 for the most common form, sCJD) (Brown, Cathala et al. 1986). Although incidence of CJD is approximately 1 per million per year, a person's lifetime risk of dying from CJD is much higher than this for several reasons. The incidence includes the entire population, including infants, children and the very old, and because most people will live to the age of peak incidence of sCJD, each individual's lifetime risk of dying from CJD, particularly sCJD, is (taking deaths from CJD over all deaths) probably around one in tens of thousands.

1.5 Pathology

Definitive diagnosis of human prion diseases is only possible through brain pathology, usually autopsy or biopsy. The typical changes seen in brain tissues of patients with CJD include prion deposition (detected by immunohistochemistry and/or western immunoblot), nerve cell loss, gliosis and vacuolation (historically called spongiform change, hence the name transmissible spongiform encephalopathies) (Kretzschmar, Ironside et al. 1996).

1.6. Early Diagnosis Research/Biomarkers

Several potential treatments for prion diseases have been identified in cell culture and animal models. Unfortunately, drugs that have been promising in cell culture have not typically been successful in animals, and the few drugs that stopped or prevented prion disease in animals were only beneficial when administered before or at the time of inoculation with prions. At best some treatments given before the onset of symptoms only delayed disease onset slightly (Trevitt and Collinge 2006; Geschwind 2009). A few studies or trials have been started and/or completed on human prion disease, using drugs such as quinacrine, doxycycline, and intracerebral pentosan polysulfate (PPS), and no clear sustained clinical efficacy has been shown (Otto, Cepek et al. 2004; Korth and Peters 2006; Bone, Belton et al. 2008; Geschwind, Kuo et al. 2010).

Almost all prion diseases progress with remarkable rapidity and patients are usually quite sick by the time their condition is diagnosed (Brown, Cathala et al. 1986). Indeed, by the time patients receive a CJD diagnosis they are often about two-thirds of the way through their disease course (Paterson, Torres-Chae et al. 2012). As treatments become available it is reasonable to assume that they might only be efficacious if given early in the disease course. In order to optimize future clinical trials, as well as to make the best use of future treatments which are likely to slow or halt disease course rather than cure already existing symptoms, it is necessary to diagnose human prion disease earlier and with greater accuracy than occurs in the general community (Tschampa, Neumann et al. 2001; Geschwind, Shu et al. 2008; Paterson, Takada et al. 2012). When life prolonging or symptom slowing treatments are made available, they will reduce the burden on both family and health care system if they

are administered as early in the disease process as possible. By the time most patients with CJD are correctly diagnosed they are quite impaired (Brown, Cathala et al. 1986) and their quality of life probably is quite low. They are often dependent for many activities of daily living (ADLs) and within a short period after diagnosis they often develop severe cognitive and motor impairment (Brown, Cathala et al. 1986). Prolonging this stage of disease would be burdensome to families and medical facilities, and is often not what patients might want. In the case of Karen Anne Quinlan who was in a persistent vegetative state for nearly 10 years, the New Jersey Supreme Court asks “If the patient could wake up for 15 minutes and understand his or her condition fully, and then had to return to it, what would he, or she, tell you to do?” (Quill 2005). End stage patients with CJD likely would not wish to remain in the extremely impaired condition they experience indefinitely – this stresses the importance of early diagnosis for when treatments are available and for patients to make informed decisions about end of life care.

In most diagnostic criteria for human prion disease, particularly WHO criteria, CSF 14-3-3 protein is considered a biomarker for probable sCJD diagnosis (WHO 1998; Collins, Sanchez-Juan et al. 2006; Sanchez-Juan, Green et al. 2006; Zerr, Kallenberg et al. 2009). Many, however, consider it to be a quite poor diagnostic test (Chapman, McKeel et al. 2000; Geschwind, Martindale et al. 2003), and generally less useful than neuron-specific enolase (NSE) or total-tau (t-tau) (Sato, Shirabe et al. 2007; Coulthart, Jansen et al. 2011; Hamlin, Puoti et al. 2012). For reasons that are not clear, data from the European CJD Surveillance network shows much better results for the CSF 14-3-3 test (Collins, Sanchez-Juan et al. 2006; Sanchez-Juan, Green et al. 2006; Chohan, Pennington et al. 2010) than do data from North America (Geschwind, Martindale et al. 2003; Coulthart, Jansen et al. 2011; Hamlin, Puoti et al. 2012). These biomarkers are likely more suggestive of rapid neuronal injury and not necessarily indicative of prion disease. Data suggests diffusion weighted (DWI) brain MRI to have much better sensitivity and specificity (Shiga, Miyazawa et al. 2004; Zerr, Kallenberg et al. 2009; Vitali, Maccagnano et al. 2011).

Indeed, several groups have taken issue with the poor sensitivity and specificity of the 14-3-3 protein (Chapman, McKeel et al. 2000; Geschwind, Martindale et al. 2003; Huang, Marie et al. 2003). Despite this, many physicians are too quick to diagnose patients with CJD based on positive 14-3-3 results (Chitravas, Jung et al. 2011; Schmidt, Wolff et al. 2011; Schmidt, Haik et al. 2012). This might be one of the causes of a high, 32%, rate of non-prion disease etiologies among biopsy and autopsy cases referred to the National Prion Disease Pathology and Surveillance Center between 2006 and 2009 for suspected CJD (Chitravas, Jung et al. 2011). Although both NSE and t-tau are more specific than 14-3-3 (Sanchez-Juan, Green et al. 2006; Coulthart, Jansen et al. 2011; Hamlin, Puoti et al. 2012), and t-tau is more sensitive (Coulthart, Jansen et al. 2011; Hamlin, Puoti et al. 2012), they are clearly not perfectly diagnostic and can still lead to devastating and dangerous false positives and negatives (See section below on Transmissibility for further discussion).

The brain electroencephalogram (EEG) in sCJD shows periodic sharp wave complexes (PSWCs) in about 2/3 of cases and is considered relatively specific for CJD (Brown, Cathala et al. 1986; Zerr, Brandel et al. 2000; Steinhoff, Zerr et al. 2004) though other conditions such as hepatic encephalopathy, Hashimoto's Encephalopathy and late stages of other neurodegenerative diseases might also show similar findings (Seipelt, Zerr et al. 1999; Tschampa, Neumann et al. 2001; Steinhoff, Zerr et al. 2004). These findings, however, often do not show up until fairly late in the disease course and are often less commonly seen in certain gPrDs and acquired prion diseases, such as vCJD (Mead 2006; Heath, Cooper et al. 2010; Heath, Cooper et al. 2011). MRI findings – cortical ribboning and hyperintensities in the caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) – are quite sensitive and specific, achieving about

95% sensitivity and 93% specificity (Shiga, Miyazawa et al. 2004; Vitali, Maccagnano et al. 2011), better than for any of the CSF biomarkers (Geschwind 2010; Forner, Wong et al. 2011; Wong, Forner et al. 2011) (Sanchez-Juan, Green et al. 2006; Hamlin, Puoti et al. 2012). Unfortunately these findings are often missed by radiologists (Geschwind, Kuryan et al. 2010; Carswell, Thompson et al. 2012). Even MRIs are not always an optimal diagnostic test as they are often expensive and can be quite difficult to obtain in CJD patients who have difficulty remaining still either due to myoclonus or cognitive impairment.

Early and accurate diagnosis is beneficial for all parties: patient, family, and society. If diagnosed in the earliest clinical or even pre-clinical stages of prion disease, patients might be able to make their own decisions about participation in research, how they wish to be cared for, end of life issues and what they would like done with their remains after they pass, rather than relying on surrogate decision makers. Patients and families might be better able to handle the terrible diagnosis and prepare for the challenges to come. Society benefits in multiple ways. Burdened hospitals and doctors do not need to support costly and time consuming unnecessary work-up. Research groups would have a greater availability of participants and will be better able to collect serial data on patients – information which will be helpful for planning future treatment trials. Given more time to consider the importance of autopsy for research, more patients and families might be persuaded to pursue this option. This would lead to larger sample sizes of subjects with definite diagnosis, better quality data for research, as well as increasing the chance that new forms of prion disease might be identified (Will, Ironside et al. 1996; Zou, Puoti et al. 2010).

Should a highly sensitive and specific test for prion disease become a reality, we must consider how this testing should be applied. Duncan et al. provide an interesting summary of the ethical complications arising with voluntary vs. compulsory testing, and universal vs. selective testing in the case of vCJD (Duncan, Delatycki et al. 2005). Universal voluntary testing would propose that all individuals who desire testing are allowed to be tested. This would allow for the maximum autonomy but might not be feasible if the test is expensive or time consuming. Universal compulsory testing, in which all individuals must be tested, violates principles of autonomy, but in the right circumstances could theoretically identify all cases of human prion disease. It is far more likely in the event of such a test's availability that those showing symptoms of suspected prion disease would be the only ones tested unless healthy individuals were at risk from carrying a PRNP mutation or having had potential exposure through medical procedure or otherwise. A reliable test would vastly change the way prion diseases and their mimickers are diagnosed with great benefit to individual and society. A positive test might have other complications, however, as it might not inform when or even if someone will develop disease. For example, a test might be positive in persons who carry prions, but will never develop disease or might die from other causes prior to prion disease.

2.0 Ethical Issues in Prion Disease

The ethical issues in prion disease are quite complex. On the clinical side, there is disagreement among clinicians about the utility of various diagnostic biomarkers and the urgent need for more definitive, minimally invasive diagnostic tests. Brain biopsies when positive are definitively diagnostic, but might sometimes be false negative (Josephson, Papanastassiou et al. 2007; Heinemann, Krasnianski et al. 2008). Many neurosurgeons or hospitals refuse to perform brain biopsies in patients with suspected CJD, due to fear of transmission to medical staff or future patients. Given the improved diagnostic capability with MRI and possibly other CSF biomarkers (Newey, Sarwal et al. 2013), the risks of performing a brain biopsy on a patient with suspected CJD probably often outweigh the benefits in clear CJD cases that have been thoroughly worked-up clinically, particularly

when no cures are available. Regarding treatment, even if a therapy were available to stop the disease, for many patients stopping, but not reversing, the disease and leaving them severely impaired might be a fate worse than death. Thus, stabilizing treatments might do more harm than good. Without any available treatments, early diagnosis of CJD might be futile, although it might help prevent accidental transmission and prepare the patient and family. It is crucial, however, to rule out other, potentially treatable conditions (Geschwind, Shu et al. 2008; Chitravas, Jung et al. 2011). In patients at risk for acquired or gPrD, if therapies were available, intervening prior to onset of clinical symptoms might be possible (Sigurdsson, Sy et al. 2003; White, Enever et al. 2003). Therapies might have toxicity and not be benign and thus it will be necessary to know when is the optimum time to treat. This might require a test that can detect the presence of prions (ideally in bodily fluids so that they can be identified without a brain biopsy) prior to onset of symptoms, which are still under development (Atarashi, Satoh et al. 2011). See Table 1 for a summary of ethical issues in prion disease, including where to find more information on those not discussed at length in this manuscript.

2.1 Issues Regarding Research in CJD

Conducting clinical research with persons with or at risk for rapidly fatal diseases incurs a specific set of ethical issues. When administering a potentially helpful drug, is it appropriate to do randomized, placebo-controlled trials? Randomized, double-blinded, placebo-controlled studies are the gold standard of clinical treatment trial design. Individuals with a rapidly progressive fatal illness (or their loved ones) might wish to try any treatment available, regardless of risks or potential failure and might be hesitant to participate in placebo-controlled trials in which the subject might not receive active drug (Braunholtz and Harris 2002). Unfortunately, observational studies often produce untrustworthy results which often do not hold up when repeated in more controlled, scientific ways, such as randomized, double-blinded, placebo-controlled studies. Determining whether a treatment is helpful, of no benefit or even harmful is best done through randomized, double-blinded, placebo-controlled studies. Unfortunately, this means that some subjects do not get active drug, which might have been beneficial (or possibly harmful!) to a patient with a fatal, rapidly progressive disease. Of course, research, by its very nature, might only help future patients. Fully randomized double-blinded and placebo-controlled trials will be necessary to determine the true efficacy of various treatments, but will this be appropriate in light of the desires of patients and their families? How does one balance the need for rigorous science that can benefit society as a whole with the potential of withholding efficacious treatment from an individual affected patient? As mentioned previously, earlier and improved diagnosis will certainly increase the power of future trials (Korth, May et al. 2001; Kennedy, Walker et al. 2002; Trevitt and Collinge 2006; Geschwind 2009).

Sulfated glycans, such as pentosan polysulfate (PPS), had been shown to have some binding to prions in vitro since the 1990s. PPS was later shown in one study to prolong survival in several animal models of prion disease when administered via a catheter directly into the brain prior to onset of symptoms, even well after inoculation. Unfortunately, in some cases, particularly at higher, more efficacious doses, there were not insignificant side-effects, including seizures and brain hematomas (Doh-ura, Ishikawa et al. 2004). In 2002 two families in the UK whose children were diagnosed with vCJD brought a legal case to the High Court of England and Wales to allow the intracerebral administration of pentosan polysulphate (EWHC 2734 (Fam) 2002). At the time PPS treatment had only been tested in animal models and it has to be given directly into the brain as it does not cross the blood-brain barrier, and therefore, was of questionable use in CJD. Indeed, Doh-Ura's work on the efficacy of PPS in animal models was not published until 2004 (Doh-ura, Ishikawa et al. 2004). After an arduous legal battle including testimonies from Doh-Ura and others in the

field the drug was administered, and though it did not cure patients, it might have prolonged their disease course. Since then observational studies with PPS in CJD have been conducted in Japan and the UK; the results overall do not suggest clear benefit, although some feel that it might prolong survival in vCJD, albeit with patients in a severely incapacitated advanced state (Bone, Belton et al. 2008); a few of the longest living vCJD patients had received intraventricular PPS, but there might have been other reasons for their prolonged course, including extraordinary level of care (Bone, Belton et al. 2008; Honda, Sasaki et al. 2012). This sets a potential precedent of patients circumventing the usual path of scientifically appropriate, randomized, double-blinded, placebo-controlled clinical trials in order to receive any available intervention.

Two formal trials with quinacrine in human prion disease were conducted; one in the USA at UCSF was a randomized, double-blinded, placebo controlled trial (Geschwind, Kuo et al. 2010), whereas the UK trial was essentially an open-label observational trial (Collinge, Gorham et al. 2009; Geschwind 2009). In the UCSF quinacrine trial, in order to increase study enrollment all study participants were offered the option of going on open-label quinacrine if they returned for their Month 2 visit. This was done for several reasons. It was felt that because the medicine was available from compounding pharmacies patients might not be willing to enroll in a study in which they might never get active drug. Furthermore, based on the UCSF preliminary observational survival data (M. Geschwind, unpublished) and the rapidity of prion disease, a difference between the placebo and active drug (quinacrine) arms would be found even with a two month treatment initiation difference. Perhaps not surprisingly, some patients elected to not enroll in the study; often they were so incapacitated that the prospect of halting the disease at that stage was undesirable. Several enrolled subjects decided not to take open label quinacrine at their Month 2 visit. Those subjects who chose not take open-label quinacrine did so for a variety of reasons. For some subjects, their caregivers felt they were too advanced. Other subjects felt they were already on active drug and did not feel the need to go on open-label (Geschwind, Kuo et al. 2010). This is similar to findings from the PRION-1 study, in which the most impaired participants were the least likely to choose to go on quinacrine (Collinge, Gorham et al. 2009).

2.2 Issues in genetic prion diseases (gPrDs)

As noted above, approximately 15% of all prion disease cases are genetic, following an autosomal dominant pattern of inheritance, with most mutations having 100% penetrance. Some, such as those due to the E200K mutation, have lower penetrance, varying from about 60% reported among Slovaks to an age dependent penetrance noted among Libyan Jews, 77% penetrance by age 70 and 96% penetrance over age 80 (Spudich, Mastrianni et al. 1995; Mitrova and Belay 2002). There are a multitude of potential ethical issues associated with gPrDs, particularly for individuals at risk, but also for those at-risk, but who find out they do not have a mutation.

2.2.1 At-Risk Research Subjects—In the search to find the earliest signs of disease, individuals who carry a prion protein gene (*PRNP*) mutation and likely will develop genetic prion disease (depending on the mutation penetrance) might provide invaluable information for research. Given the virtual 100% penetrance of most *PRNP* mutations, most persons with *PRNP* mutations ultimately will become symptomatic. By carefully tracking and studying these persons, it might be possible to identify the earliest features of their disease. This information might help future gPrD patients when treatments are available. Additionally, these presymptomatic gPrD individuals thus might be a model for prodromal and preclinical phases of much more common prion diseases, such as sCJD. At-risk research participants are invaluable to clinical prion research, yet it is unlikely that they will receive any direct benefit from their participation; with most clinical research the goal is primarily to help

future patients (Pierce 2010). Persons at-risk for gPrD are an inherently vulnerable population and their position in the research model is fraught with several ethical considerations. Involving such individuals in research that exposes them to greater than minimal risk requires a greater consideration of the ways in which at risk and asymptomatic mutation positive individuals might constitute a particularly vulnerable research population. Though currently healthy, they face an almost certain incurable disease. Their personal motivation to participate in research might make them more likely to be permissive of higher than minimal risk activities, including lumbar punctures and drug trials (Pierce 2010). Because of the rarity of gPrD, individuals with *PRNP* mutations might feel pressured by family or by researchers to participate in research that often involves some risk, both physical and more importantly psychological. Physical risks for participation in clinical research might range from possible complications associated with lumbar punctures and MRI scans (including post-LP headaches and bouts of claustrophobia) to an unknown range of side-effects that might be associated with treatments used in human clinical trials. The psychological consequences perhaps are harder to define, but are important. Some at risk individuals might suffer negative psychological consequences from participation. This might be due to increased worry about their future, stress from research testing (such as difficulty with aspects of the neurological or neuropsychological testing) or other factors. Having an at-risk status for a rare genetic disorder places additional impetus for participation in research on the at-risk person.

It should be determined that the at-risk research patient is participating of their own volition and is not being coerced. Family members, especially parents who have seen various family members die of genetic disease, children who are the next generation of at-risk individuals, and spouses who fear losing their partner, might be inadvertently coercive to those eligible for research. The potential good that is to be gained from ongoing research efforts might have more direct benefit for family members than for mutation positive research participants, who, depending on their age, will likely succumb to the disease before treatments are developed. Allowing research participants adequate time to discuss participation with their family, reflect on their possible participation, as well as having the researchers provide sufficient information, might help allay outside influential forces.

Due to the pressures at-risk individuals often find themselves under to participate in research, it is especially necessary that they understand the potential risks and benefits to themselves, both personally and in terms of their relationships with their family members. It is assumed, in a bioethical framework, that for a person to make an ethical decision about his or her own treatment they must be able to make decision intentionally, with understanding, and without outside controlling forces that may influence their decisions. In other words, they must be able to provide informed consent. But in diseases that have potentially serious implications for genetically related kin of a person diagnosed with a fatal illness, the ethical questions go beyond the subject/individual, as decisions might affect others. The idea of informed consent in cases of persons with or at risk for gPrD is complicated by notions of individuality that ignore how decisions one person makes about the “right to know” his or her gene status affect family and possibly others. When one person's desire for information violates another person's desire to not know, how must researchers proceed?

2.2.2 Presymptomatic genetic testing—Individuals at risk for gPrDs are able to undergo genetic testing (DNA test) to see if they have inherited a *PRNP* mutation. The decision to test or not to test should not be taken lightly: no matter the outcome, testing has very serious implications for the individual and all of their family members.

Each biological child (or sibling) of an individual with gPrD has a 50% risk that they also have inherited a *PRNP* mutation. Prior to, or without, being tested, at-risk persons live in a liminal state, in which they exist as both potentially positive and potentially negative. The at-risk child might represent the fear of the parent with the mutation that they have passed on the mutation to their child, and the fear of the gene negative parent that the devastating disease they see or will see in their spouse will be replicated in their children. It is considered standard of medical care that individuals wishing to undergo genetic testing also participate in appropriate genetic counseling, such as following a Huntington's disease (HD) protocol for autosomal dominant neurological diseases (International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea 1994; Shively, Scher et al. 2012), to give everyone an opportunity to consider how their genetic status might impact their life.

Following the guidelines established for genetic testing for HD, in order to be tested for gPrD, one must be over the age of 18 and participate in a series of counseling sessions, aimed at determining one's readiness and emotional capacity to hear the results of the test. Predictive testing of minors (those under age 18, depending on the country) is usually not performed unless the individual is symptomatic or has another compelling reason for testing (e.g., is going to have children) (International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea 1994; Charlis, Cagan et al. 2012). In addition, in most regions, minors cannot be considered legally competent nor potentially 'fully aware' of the risks and benefits of testing (Holt 2006; Sparbel, Driessnack et al. 2008).

Some of the most often cited benefits or reasons to know one's gene status include: A relief from the uncertainty of not knowing or a need for certainty, practical (e.g. financial, employment, educational) decisions, reproductive decisions, and being able to inform one's children of their potential risk for gPrD. Common reasons for not testing include: a perceived inability to cope with the test result, the lack of current treatments for gPrD, concern about the reactions of family members and friends, and being happier living with uncertainty than with the certainty of an unwanted result (Evers-Kiebooms and Decruyenaere 1998; Taylor 2004). In the at-risk gPrD cohort at the UCSF prion disease research program, 60–70% of at-risk individuals coming in for testing want to know their gene status. This is much higher than for other autosomal dominant neurodegenerative diseases, such as Huntington's disease (Kong, Surewicz et al. 2004). This discrepancy might in part be due to sample bias; those who come in to participate in research are generally more willing and able to confront the possible eventuality of their illness. Another reason why more persons at-risk for gPrD might wish to know if they carry a mutation is that for most gPrDs, onset usually is later in life than for HD, for example. At-risk persons might therefore feel there is more time for a cure or that they might succumb to other illnesses prior to developing gPrD.

There are myriad problems facing the at-risk person who wishes to know their gene status. With the introduction of the Genetic Information Nondiscrimination Act (GINA) in the United States in 2008 (2008), many of the problems facing asymptomatic persons in this country with pathological genetic mutations were vetted. GINA protects against discrimination and harassment based on genetic information and protects the confidentiality of genetic information in cases of hiring, firing, job placement, and promotion decisions (2008). It also stipulates that insurance companies and group health plans cannot deny coverage or require higher premiums of healthy individuals with a genetic predisposition to developing a disease. GINA does not, however, ensure that individuals seeking individually purchased long-term care insurance or disability insurance will face no discrimination (e.g., just as there are laws in the US against racial discrimination, laws alone do not ensure that

discrimination does not occur!). Widespread education concerning the ways in which genetic information is protected under law might encourage that these laws be followed (Prusiner 1998; Erwin 2008).

Obtaining long-term care and/or disability insurance prior to receiving genetic results is an important issue to discuss with at-risk persons prior to genetic testing or persons receiving genetic results. Once a person knows their genetic results, when applying for long-term care and/or disability insurance they might be asked if they have any predisposing conditions; if one already has the genetic test results, legally they must state this. If one, however, has not received their results and does not know their genetic status, they truthfully can state that they are not aware that they have any such pre-existing condition. Generally, it is strongly encouraged for all at-risk subjects to obtain long-term care and/or disability insurance prior to receiving their PRNP results; if they find they do not have a mutation, they can always cancel the insurance policy, whereas obtaining such insurance is highly troublesome post results disclosure (Hudson, Holohan et al. 2008; Appelbaum 2010; Feldman 2012).

Even a gene-negative test result can have complicated outcomes, including but not limited to a need to readjust one's view of self as "at-risk", a change in one's role within the family system which has been previously characterized by the shared bonds of genetic risk, and survivor guilt (Sobel and Cowan 2000). For those who test gene-positive, there are significant challenges, which might be made worse by the intimate knowledge many at-risk persons have of the course of the illness in other family members. Importantly, "there is no escape after predictive testing: once a person receive[s] the information, there is no way of obliterating the knowledge" (Evers-Kiebooms 1987). Individuals should be encouraged to think seriously about why they might want or not want to know their mutation status. They should consider how their life might change if they have a mutation or if they do not have a mutation.

Due to the increased risk of depression as well as attempted and completed suicide among individuals at risk for some incurable neurodegenerative diseases (Naj, Jun et al. 2011; Shively, Scher et al. 2012), a psychiatric assessment, including assessment of depression and suicide risk, is needed as part of the Huntington's disease protocol for genetic testing. If an at-risk person admits to, or is felt by the medical staff, to be at risk for suicide, procedures should be in place for handling this situation. In most cases, such a person should not be tested, or if already tested, the results should not be given until a depression and/or suicide prevention management plan is in place (Almqvist, Bloch et al. 1999).

A grandchild of someone with gPrD has a theoretical 25% chance of having the mutation; if their parent has a *PRNP* mutation, their risk increases to 50%, whereas if their parent does not have a mutation, their risk of developing gPrD is essentially zero (they have the same risk of developing other forms of CJD as anyone else in the population). If the parent does not wish to be tested (i.e. does not wish to know their mutation status), however, there are further issues to contend with. If the child with 25% or 50% risk tests positive, the parent and/or grandparent is guaranteed to have the mutation. This can cause serious rifts within families, as one person's right to know can violate another person's right not to know (Black and McClellan 2011). For example, the adult grandchild of a gPrD patient might wish to know their genetic status, without the parent (the child of the gPrD patient) desiring to know theirs. After providing basic genetic counseling to this individual, this grandchild must be urged to have a conversation with their parent to discuss the fact that if they (the grandchild) tested positive for a gPrD mutation, their parent would necessarily carry the mutation as well. The family should be encouraged to discuss how they would handle this situation to protect the child and the parent's right to know or not know. The genetics of gPrDs can be difficult for families to grasp without the aid of a medical professional trained in these

issues. Unintentional disclosure usually can be avoided if researchers and families work together to assure that all involved know the implications of know any family member's genetic test result.

Clinicians conducting research in presymptomatic gPrD might encounter additional ethical dilemmas. A comprehensive neurological examination might detect abnormalities that could be within the range of normal, not be real (e.g., not neurologically-based, psychosomatic) or might be abnormal and real, but unrelated to prion disease. For example, a subject with a known gPrD mutation whom we have seen in our center several times believed they had begun to experience the same early sensory symptoms of gPrD that their parent had experienced. The subject also had subtle abnormal motor neurological findings on exam. We could not be certain that the neurological findings and her sensory complaints were significant. As we were unclear if the neurological findings were truly abnormal we did not mention them to the subject. When the subject returned one year later for a follow-up visit, both the sensory changes and neurological findings were no longer present. Often it is difficult to ascertain whether changes are real or psychosomatic. A young patient with a known mutation, but likely many years from disease onset based on the family history, presented with complaints of new onset incoordination and had subtle motor abnormalities on exam, which were not definitively neurological. Stress reduction techniques were recommended, and these problems resolved.

A different set of problems might arise when an at-risk individual allows the physician/researcher to determine their gene status, but the individual does not want to know the gene test result. In one case, an at-risk patient from a gPrD family had some asymmetric motor symptoms that were difficult for the neurologist to determine if they were functional or organic, and if they were neurological it was not clear they were related to gPrD. The patient believed they had symptomatic gPrD and had begun to take an off-label experimental medication, but decided they did not want to know their *PRNP* status from the genetic testing already sent by physician (with the patient's consent). The patient was informed that this symptom might not be due to prion disease and it should be evaluated further. The physician later found that they were negative for a *PRNP* mutation. This placed the physicians in a quandary. They needed to balance this individual's right not to know their *PRNP* status, while ensuring the patient did no harm to themselves by taking an unnecessary medication. In this case, the physicians did not inform the patient of their *PRNP* status, as it was felt that the off-label medication was of little risk to the patient. As physicians and researchers, how does our knowledge intersect with our participants' rights? If the motor findings in the patient are real and caused by a separate medical issue, what is our responsibility to inform patients? Medications might have potentially significant side effects; if there are proven treatments for the actual cause of symptoms, is it ethical to allow patients to continue to take possibly harmful and likely unhelpful medications? Is it sufficient to encourage the patient to have their problem worked up further in case they do not carry a *PRNP* mutation?

2.2.3 Family planning issues—One of the main reasons why children of individuals affected by gPrD chose to know their gene status is for family planning. Some at-risk (or even mutation positive) parents have decided not to have children because of the relatively high risk (50% if they have *PRNP* mutation), of passing on the mutation to their offspring. Technological advances, however, now allow for multiple options for individuals at risk for genetic disease, whether or not they wish to know their genetic status (Brown, Cervenakova et al. 1994). It is now possible for a mutation carrier to virtually guarantee that their offspring do not have a *PRNP* mutation through in vitro fertilization and pre-implantation genetic screening of the embryo. This can also be done in a manner so that an at-risk parent does not have to know whether they carry the mutation, but can be guaranteed that their

offspring will definitely not have the mutation. One such technology is pre-implantation genetic diagnosis (PGD).

2.2.3.1. Pre-Implantation Genetic Diagnosis (PGD): Pre-implantation genetic diagnosis (PGD) occurs during *in vitro* fertilization (IVF) and is a procedure in which genetic markers from about a three-day-old embryo are examined for genetic anomaly, sex, or a number of other traits. Parents are then able to choose which embryo or embryos they wish to have implanted (Spar 2006). In cases of gPrDs, parents with a known risk of passing on a *PRNP* mutation (e.g., are at-risk for gPrD) to their children can elect to only implant embryos not carrying the gene transmitted from the carrier parent. This technology stemmed from Edwards and Gardner's research in 1967, in which they were able to accurately determine the sex of rabbit embryos (Edwards and Gardner 1967). The first live birth following PGD occurred in 1990, with the embryos being tested for cystic fibrosis (Handyside, Lesko et al. 1992).

Whereas there are specific ethical issues that are relevant to PGD for individuals wishing to spare their children an adult-onset, fatal, highly (or even fully) penetrant *PRNP* mutation, there also are many important ethical issues raised with the PGD procedure itself. Ethical issues concerning PGD as a procedure itself include questions of when life begins, what to do with affected (e.g. mutation positive) cells, the potential inaccuracy of genetic testing, and what to do in cases of mutations that are not fully penetrant, such as for some E200K mutations and BRCA genes. Some people feel that PGD is a form of eugenics and argue that by the time a child born with an adult onset disease mutation reaches the age at which they may begin to show symptoms, cures might have been discovered. Embryos with mutations usually are destroyed or used for research (if consent given); this is a decision that might be difficult for parents who see those embryos as potential or actual children. As PGD technology exists, it is important to consider whether individuals who know they have a *PRNP* mutation, or those who know they are at risk but choose not to know, and decide not to undergo PGD are doing harm by allowing each of their children a 50% risk of inheriting the mutation. PGD, however, is also quite expensive (in the US, it is typically in the \$10–15,000 range and not usually covered by insurance) and beyond the financial means of many families. There is the potential of further stigmatizing individuals who are either unable or unwilling to undergo PGD, placing the 'blame' for their child's disability or illness on the parent who had no control of their own genetic fate (Bredenoord, Dondorp et al. 2009).

Although predictive testing of an asymptomatic minor is considered morally irresponsible by the medical community (Huntington's Disease Society of America 1994; International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea 1994), prenatal *PRNP* testing is not legally restricted. If a couple continues a pregnancy in which they know the fetus to have a genetic mutation, this raises several ethical issues. The child has been tested without his or her consent. Even if the parents wait to inform the child of their mutation status until they become an adult, this might still be construed to be a violation of the individual's right to be tested or not, regardless of whether they want to know the test results. An even more concerning scenario occurs if the child is informed of their gene status as a minor. For an informative summary of PGD and some of the issues involved for genetic disorders as discussed by a couple who has been through the procedure, we recommend resources through the CJD Foundation (<http://www.cjdfoundation.org/presentations/Bradley-Amanda-Kalinsky.pdf>) (<http://www.neuropion.org/en/videos-cjd2011-kalinsky.html>).

With the advent of PGD, as well as fetal testing paired with therapeutic abortion, *PRNP* mutations essentially can be eradicated from a lineage in one generation. To our knowledge, there has been one documented case of molecular genetic testing of a fetus *in vivo* (Brown,

Cervenakova et al. 1994). The fetus fortunately tested negative for that mutation, and the question of whether to terminate the pregnancy due to mutation status was no longer necessary. The decision to pursue such options is highly personal and might range greatly even within families as each individual has their own ethical, moral, and religious standards. Making sure that all at-risk individuals know about the availability of options provides the opportunity to make well-informed choices.

2.3. Incorrect Diagnoses

In part because of a lack of definitive premortem, minimally-invasive diagnostic test, both false positive and false negative incorrect diagnoses are quite common in evaluating patients with rapidly progressive dementia (Seipelt, Zerr et al. 1999; Tschampa, Neumann et al. 2001; Chitravas, Jung et al. 2011; Paterson, Torres-Chae et al. 2012). Each of these misdiagnoses has potentially grave implications for individual, family and society.

2.3.1. False positive Diagnoses—Perhaps most devastating for the individual and family is a false positive diagnosis, when a patient is misdiagnosed as having CJD yet they have another, non-prion disorder, which in some cases might even be treatable if not curable. As CJD in all its forms is a universally fatal disease with no cure, when a physician incorrectly diagnoses CJD, often no further workup occurs. In such cases, the patient with a potentially treatable or even curable condition might not receive further intervention and be allowed to progress without treatment or even pass away. Many non-prion conditions might present similarly to CJD (Seipelt, Zerr et al. 1999; Tschampa, Neumann et al. 2001; Geschwind, Shu et al. 2008; Geschwind, Tan et al. 2008; Chitravas, Jung et al. 2011; Sala, Marquie et al. 2012; Newey, Sarwal et al. 2013). Indeed, CJD is often referred to as “the great mimicker,” because it presents (particularly in the early disease stages) similarly to many other neurological conditions and vice-versa – many non-prion conditions mimic CJD (Geschwind, Haman et al. 2007; Geschwind 2010). Although many common conditions misdiagnosed as CJD are also incurable, including other neurodegenerative diseases and vascular dementia (Tschampa, Neumann et al. 2001; Geschwind, Shu et al. 2008; Schmidt, Redyk et al. 2010; Schmidt, Haik et al. 2012), a study by Chitravas et al. found that of non-prion conditions mistakenly referred to the U.S. National Prion Disease Pathology and Surveillance Center (NPDPSC) between 2006 and 2009, 23% (n=71) were potentially treatable, in some cases even curable (Chitravas, Jung et al. 2011). Only eight of these potentially treatable cases met the World Health Organization (WHO) criteria for probable CJD (WHO 1998), and another 13 for possible CJD. More than 50% of cases, however, had an elevated CSF 14-3-3 protein, often leading to the misdiagnosis as CJD. This again highlights the lack of specificity of this CSF biomarker and the need for more sensitive and specific biomarker assays, as well as the need for education of physicians who see patients with rapidly progressive dementias to understand the limitations of such biomarkers. Whereas data suggests the most common conditions misdiagnosed as sCJD were other incurable (but sometimes treatable) neurodegenerative conditions, the second most common category of misdiagnoses were autoimmune conditions, many of which were readily treatable, and even curable (Geschwind, Shu et al. 2008; Rosenbloom, Smith et al. 2009). The most important diseases to consider when a patient presents with a rapidly progressive dementia might be remembered via the mnemonic, VITAMINS: Vascular, Infections, Toxic-Metabolic, Autoimmune, Metastases/neoplasm, Iatrogenic, Neurodegenerative, and Systemic/Seizures. As many of these etiologies are potentially treatable, it is imperative that other causes be ruled out before a diagnosis of prion disease diagnosis is given (Geschwind, Shu et al. 2008; Geschwind 2010).

2.3.2. False Negative Diagnoses—A false negative diagnosis for CJD carries with it a different set of problems than false positive diagnoses (Paterson, Torres-Chae et al. 2012).

Perhaps most salient from a public health perspective is potential contamination and the risk of subsequent transmission. As discussed in the section “Acquired CJD,” cases of iatrogenic CJD have occurred by transmission from sCJD and vCJD patients (Brown, Preece et al. 2000; Peden, Head et al. 2004; Brown, Brandel et al. 2006), and there is a theoretical risk of transmission of gPrD (Tateishi and Kitamoto 1995). If a patient has any type of invasive neurological procedure including a brain biopsy and thorough prion decontamination measures are not taken on all surgical instruments used, other patients exposed to that contaminated neurosurgical equipment are at risk for transmission of prions, and developing iCJD. Even surgical equipment used on non-CJD patients may be a source of potential transmission if it comes into contact with equipment used on CJD patients during the cleaning process.

Members of the patient's medical-surgical team, as well as funeral home personnel and pathologists might put themselves at unnecessary risk during procedures involving bodily fluids and tissues if they do not know to follow the proper risk reduction procedures (<http://www.cjdfoundation.org/pdfs/enbalmersguide.pdf>)(WHO 2003).

One of the problems with a false negative diagnosis is that families are not able to prepare for the disease course and cannot adjust their expectations of their loved one's prognosis. Without the correct diagnosis, families and physicians might continue to look for a curable condition, trying to extend the patient's life, not realizing that there is no cure. They might not make adequate preparations for caring for the patient as they advance (e.g., hospital bed, re-arranging the house, 24×7 care, etc...) or be prepared for the patient's passing and post-mortem arrangements (e.g., funeral, burial, cremation, etc...).

Missing a diagnosis of gPrD has serious implications regarding appropriately informing relatives of their own (or their children's) risks as well as for possible iatrogenic transmission. As noted above, in a European study, a surprisingly high percentage (60%) of individuals with gPrD had no positive family history of CJD, although in retrospect many had a family history of misdiagnosed Alzheimer's disease, Parkinson's disease, or other movement or dementia related illness (Kovacs, Puopolo et al. 2005). As there is a theoretical risk of transmission of gPrD by transfusion of blood products, persons at-risk for gPrD should not donate blood until they know of their *PRNP* gene status and are found not to have a mutation (see Transmission section below). A false negative diagnosis leaves these persons unable to make fully informed choices about their health, their reproduction, and their future more generally.

2.4. Transmissibility

The transmissible nature of prion diseases requires different ethical considerations than other forms of dementia or rapid fatal disease. Prions have been shown to pass from animals to humans, such as in the cases of vCJD mentioned above, and between humans in the form of iatrogenic CJD. Some of the most pressing concerns about the transmissibility of prion diseases are in regards to interspecies transmission, the theoretical transmissibility of gPrD, instances of iatrogenic exposure to prions, and public perception of risk.

2.4.1. Interspecies Transmissibility—Until the mid-1990s, cross-species transmission of prion disease outside of the laboratory was thought to be highly unlikely. The occurrence of BSE in cattle (being fed prion contaminated sheep) and subsequent outbreak of vCJD has changed attitudes on the risk of such forms of CJD.

Media hype surrounding vCJD in the 1990s and 2000s has direct impacts on public perception of human prion disease today. Unfortunately, the media often refers to patients with a CJD diagnosis as having “mad cow disease.” This not only is incorrect, but giving a

patient the diagnosis of an animal disease has its own negative, often even demeaning, connotations. Although BSE and various forms of CJD are both prion diseases, they are different conditions and in different species. Families might unduly worry that they have been exposed to a causative agent through food when in fact the vast majority of CJD cases are sporadic or genetic in etiology and not acquired, particularly through food exposure. Barring iatrogenic exposure, cases of sCJD and gPrD generally are not cause for widespread public health concern. A novel case of vCJD acquired in a country previously not known to have vCJD, however, would require extraordinary management by public health offices. For example, three cases of vCJD have been identified in the United States and two in Canada, all of which were thought to have originated outside of North America (Belay, Sejvar et al. 2005; Holman, Belay et al. 2010; UK National CJD Surveillance Unit 2012). A domestically-acquired vCJD case in the United States would have grave implications for healthcare and the cattle industry.

Though, as previously mentioned, there is no evidence that the CWD rampant in the northwestern United States is transmissible to humans, an issue of potential ethical concern is whether hunters should be required to test all at-risk carcasses for prion disease. No state currently requires testing of animal carcasses, but many endemic states offer such testing. This testing is done despite the lack of knowledge as to whether or not CWD is transmissible to people. Laboratory data suggests transmission is unlikely, but a theoretical possibility (Sandberg, Al-Doujaily et al. 2010; Wilson, Plinston et al. 2012). CWD testing of animal carcasses also is not without hardship for hunters, however, who have to drop off the carcass head at designated State facilities and are informed several days later of test results. Although the testing is free, it adds a level of complexity to the hunting process leading many to not seek out testing for their carcasses. This meat possibly is then provided to others, potentially exposing them to an unknown risk of transmission. What should be done in cases in which persons have already consumed the meat who later find out the animal had CWD? Though the risk seems minor, should the person be informed that they now have a theoretical risk of having acquired a fatal disease that might not appear for years or decades, or might never occur? The psychological consequences of this knowledge need to be weighed against the need for public health surveillance.

2.4.2. Iatrogenic CJD and Theoretical Transmissibility—Because it is not yet possible to test levels of transmissibility in humans, there is much uncertainty of exactly how transmissible prions are iatrogenically or between species. A Cochrane review by Ryan et al. (Ryan, Hill et al. 2011) discusses the ethical implications of post-prion exposure notification, especially in light of the fact that this disease cannot currently be screened for. Using previous studies on communicating bad news to cancer patients, as well as to individuals infected with HIV or Hepatitis C, they conclude that “the balance between precautionary public health priorities, the individual’s rights, and the potential harms of notification of CJD or vCJD risk exposure [...] remain contentious” (Ryan, Hill et al. 2011). They noted that uncertainty of acquired risk for possible future disease in many forms of CJD would be a reason for non-disclosure, but that there is a trend toward more openness with patients and families about facts surrounding potential adverse events. Additionally, given that it is now clear that vCJD can be transmitted through blood products (Peden, McCardle et al. 2010) there is greater need from a public health perspective to disclose risk to patients and families. How can we mitigate the anxiety and stress of learning you have been exposed to a life-threatening disease agent while stopping further potential iatrogenic transmission? There has been very little research in how to best notify and support persons at risk for iatrogenically transmitted CJD. Long term support of at risk individuals is paramount to their continued mental health, especially in light of the fact that though most surveyed individuals express a desire to know their potential risk from iatrogenic exposure, a small but significant portion do not.

Though there have not been any proven instances of human to human transmission of genetic forms of prion disease, there is a theoretical risk based on animal models (including transmission of human gPrD to animals). As genetic testing and results disclosure clearly cannot be required, there is a theoretical risk of prion transmission from symptomatic, and even asymptomatic, *PRNP* mutation carriers to other persons receiving or exposed to blood, organ, or other tissues from the *PRNP* mutation carrier who do not know their mutation status or who do not understand the risks associated with being a carrier. Due to this it is currently recommended that all relatives of a person diagnosed with CJD not donate blood, organs, or tissues. Individuals who have spent more than three months in the UK between 1980 and 1996 are also banned from donating blood or blood products in the US (FDA 2010). This ban might cause undue concern for these potential donors who might perceive the ban as an indication that they are at risk for vCJD. Although not specified in the blood donation center instructions, once a patient is determined not to have gPrD through *PRNP* analysis, any of their biological relatives should then be able to donate blood as they are no more at risk of having CJD than anyone else in the population. Unfortunately, our experience has shown that most personnel staffing blood donation centers do not understand this concept. This is particularly detrimental because over exclusion of potential blood donors might lead to shortages in available blood products. This possible risk must be conscientiously weighed against the theoretical benefit of keeping CJD blood out of the donor blood supply.

When it has been determined, as in the aforementioned cases at Emory and Greenville hospitals in the USA, that patients have been potentially exposed to prions, how should medical facilities proceed? The risks of not informing patients of their potential at risk status include the possibility of further transmission to others and the unnecessary work-up that will be required should they ever develop neurological symptoms. If patients are told of their risk, the psychological consequences could be extreme for the patient and their family.

What is the responsibility of the researcher or medical provider who, in the course of a study or patient visit, finds information that is salient to general public health? In one case, a symptomatic patient seen for research consented to genetic testing, but after the individual had passed, their family decided not to receive the results of the test. The genetic test showed this patient had a *PRNP* mutation and thus had gPrD. As the family had requested not to know the outcome of the genetic test researchers could not inform family members of their risk for gPrD. As there is a theoretical risk of prion transmission via blood transfusion even from individuals who are presymptomatic gene carriers, members of this family might have donated blood without knowing that it is not advisable to do so. Fortunately, due to potential risk of transmitting disease, all persons at-risk for gPrD as well as family members of a patient who did not have genetic testing or decided not to know their *PRNP* mutation status are instructed to not donate blood. This highlights the importance of all patients receiving genetic counseling and being told that until they know the result of the genetic test in an individual with CJD, they should act as if it is gPrD for purposes of blood and tissue donation – all biological relatives should not donate blood or tissue.

2.4.3 Public Perception of Risk—What should protocol be in regards to notifying people who might have been exposed to prions? The CDC website states, “destruction of heat-resistant surgical instruments that come in contact with high infectivity tissues, albeit the safest and most unambiguous method as described in the WHO guidelines, may not be practical or cost effective” (WHO 2003; WHO 2006). Considering the high costs associated with some of the expensive equipment necessary to perform a brain biopsy or other procedures on CJD patients, these concerns are appreciable. Due to the high volume of patients with known prion disease seen at UCSF, it was decided that all neurosurgical equipment used in a neurosurgical procedure in a patient with suspected CJD would be

incinerated, rather than decontaminated per WHO or equivalent protocols, in order to prevent the risk of any transmission (UCSF Medical Center 2012). This conservative approach was done in part for practical medical-legal reasons; given the high volume of patients and the incidence of CJD in the population, statistically it was likely that at some point a patient who had been through the UCSF system would develop CJD. Even a frivolous lawsuit could cost the medical center millions. Given the few brain biopsies performed on suspected CJD subjects, it is felt to be cost-effective to ensure no possible transmission by destroying equipment after use, rather than decontaminating it according to WHO protocols and returning it to use as is done in many other medical centers.

The workup necessary to determine the cause of a patient's rapidly progressive neurological condition can be extraordinarily costly and might pose a large burden on an already strained hospital budget. At the same time, in patients with equivocal diagnoses, invasive medical procedures might be the only thing standing between a correct diagnosis and a preventable death. In one case, a patient with an RPD was referred to research with a presumed CJD diagnosis. The patient's presentation overlapped clinically with CJD, but a thorough work-up for RPD (Geschwind, Shu et al. 2008) revealed enlarged paratracheal lymph nodes and a paraneoplastic panel identified a positive paraneoplastic antibody often found in lung cancers. Oncology would not treat the potential cancer without tissue evidence, but the medical center only had two flexible bronchoscopes required to do the procedure safely and with a high degree of success. Due to CJD precautions, the scope used in the procedure would be cleaned and temporarily isolated/decommissioned until CJD was ruled out in the patient, leaving only one remaining scope available for the entire medical center, which was felt to be unacceptable. The treating team was unable to convince the various services involved to do the biopsy. Eventually, after several days the medical center realized it was more cost-effective to purchase an additional scope than to keep the patient in the hospital awaiting a diagnosis. The biopsy revealed lung cancer and later blood tests confirmed a paraneoplastic disorder, which was successfully treated and the patient was discharged home where they recovered substantially.

2.5 End of Life Issues

Human prion diseases are fatal in all cases, with the majority of patients dying of aspiration pneumonia. End of life care becomes imminently important in all cases. After diagnosis of CJD, families should be encouraged to prepare for their loved one's decline and death. This includes preparing for a loved one's increasing disability, for the medical care they are to receive as they near death (such as hospice), and whether or not to pursue autopsy. It is useful to encourage all families to look in to palliative and hospice care for their loved one as soon as possible.

2.5. 1. Autopsy—It is highly recommend that families pursue brain autopsy for a variety of reasons. For many families, autopsy-confirmed diagnosis of CJD might provide closure and allow for some peace of mind knowing that there was nothing further they could have done to save their loved one. It is also a way to contribute to research; CJD tissue is rare and is a vital part of continued research on prion diseases. In addition, it allows for continued surveillance, especially of atypical findings indicative of vCJD or of new forms of acquired prion disease, such as the theoretically possible transmission of CWD to humans (Zou, Puoti et al. 2010). In the U.S. (www.cjdsurveillance.com) and many other countries, autopsies in suspected CJD cases are arranged and paid through government CJD surveillance program (Louie, Gavali et al. 2004; Ladogana, Puopolo et al. 2005).

Families that wish to have an autopsy on their loved ones, however, often meet resistance from embalmers, cremators, and others who may come in contact with bodily fluids and

tissues Unfortunately, the major barrier for acquiring autopsies in CJD cases is family reluctance (Louie, Gavali et al. 2004). There is a significant amount of misinformation among these professionals as to the risk of transmission. As researchers have the most benefit from obtaining tissues from individuals with prion disease, at least some of the imperative to teach about actual and perceived risks should be theirs.

3.0. Conclusion

Although prion diseases are rare, they present a multitude of ethical quandaries, many of which are quite relevant to other similar, uniformly fatal, yet slower progressive, neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, Frontotemporal Dementia, and related disorders. In fact, recent data suggests that although prion diseases are rare, their overlap with other neurodegenerative is significant; these other conditions might spread in the brain by a prion-like mechanism (Prusiner 2012). Thus, what is learned through research in prion diseases might have profound implications for more common neurodegenerative diseases. This information often helps patients and families to be more interested in helping with research.

Continued consideration of the ethical issues implicit in all aspects of prion disease research and care, as well as support and funding for research in prion diseases, is vital. As new discoveries are made, this field will change greatly, especially should new treatments or cures be discovered. When this happens, a renewed look at the ethical issues salient to CJD will be necessary.

Abbreviation List

CJD	Creutzfeldt-Jakob Disease
UCSF	University of California, San Francisco
RPD	Rapidly Progressive Dementia
TSE	Transmissible Spongiform Encephalopathy
sCJD	Sporadic CJD
gPrD	Genetic Prion Disease
fCJD	Familial CJD
vCJD	Variant CJD
iCJD	Iatrogenic CJD
BSE	Bovine Spongiform Encephalopathy
CWD	Chronic Wasting Disease
GSS	Gerstmann–Sträussler–Scheinker
FFI	Fatal Familial Insomnia
OPRI	Octopeptide Repeat Insertion
FDA	Food and Drug Administration
WHO	World Health Organization
CDC	Centers for Disease Control
NSE	Neuron Specific Enolase
DWI	Diffusion Weighted imaging

FLAIR	Fluid Attenuated Inversion Recovery
PPS	Pentosan Polysulphate
HD	Huntington's Disease
GINA	Genetic Information Nondiscrimination Act
PGD	Preimplantation Genetic Diagnosis
NGT	Nasogastric Tube

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Highlights

- We discuss the balance between individual rights and public health concerns in prion diseases
- Autosomal dominant gPrDs require extra considerations e.g. at risk family members
- Prion diseases are transmissible – public safety is of utmost concern
- Correct and earlier diagnoses will increase research capabilities

Table 1

Summary of major ethical issues in prion disease and where addressed in text

Research	• Conducting randomized, placebo-controlled clinical trials in fatal disease	Section 2.1
	• Psychological consequences of research into identifying early disease biomarkers, particularly among genetic prion disease subjects, when no treatment yet available.	Section 2.1
Genetic Prion Disease (gPrDs)	• Establishing policy on managing and reducing risk of potential transmission with families not wishing to receive genetic results.	Section 2.3.2
	• Managing release of genetic information, particularly when all family members not in agreement.	Section 2.2.2
	• Possible coercion of individuals at-risk for gPrD to participate in research	Section 2.2.1
	• Family planning in the context of autosomal dominant disease	Section 2.2.3
Incorrect Diagnoses	• Clinical and radiological misdiagnoses and consequences for patients, families and medical system.	Section 2.3
Transmissibility	• Delay of appropriate medical intervention for fear of prion contamination of limited medical equipment required for other patients	Section 2.4.3
	• Managing release of information with potential iatrogenic exposure when transmission risks are unclear and carry possibly severe psychological consequences.	Sections 1.2.3.3 and 2.4.2
	• Managing possible interspecies transmission of hunted animals with CWD	Section 2.4.1
End of Life	• Difficulty in obtaining autopsies due to fear from the medical profession	Section 2.5.1
	• When or whether to help families “let go” and avoid life-prolonging measures in a uniformly fatal disease.	Not addressed in this manuscript. For more information please see (Panegyres 2008) and our website at http://memory.ucsf.edu/cjd
	• Questions concerning quality of life and prolonging survival in patients with advanced disease.	Section 1.6 For more in depth information please see (Panegyres 2008)

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