To Be Argued By:
ALAN A. PFEFFER
Time Requested: 5 Minutes

APL-2016-00129
New York County Clerk's Index No. 151162/15

Court of Appeals
State of New York

SARA MYERS, STEVE GOLDENBERG,

Plaintiffs,

ERIC A. SEIFF, HOWARD GROSSMAN, M.D., SAMUEL C. KLAGSBRUN, M.D., TIMOTHY E. QUILL, M.D., JUDITH K. SCHWARZ, PH.D., CHARLES A. THORNTON, M.D., and END OF LIFE CHOICES NEW YORK,

Plaintiffs-Appellants,

—against—

ERIC SCHNEIDERMAN, in his official capacity as ATTORNEY GENERAL OF THE STATE OF NEW YORK,

Defendant-Respondent,

JANET DIFIORE, in her official capacity as DISTRICT ATTORNEY OF WESTCHESTER COUNTY, SANDRA DOORLEY, in her official capacity as DISTRICT ATTORNEY OF MONROE COUNTY, KAREN HEGGEN, in her official capacity as DISTRICT ATTORNEY OF SARATOGA COUNTY, ROBERT JOHNSON, in his official capacity as DISTRICT ATTORNEY OF BRONX COUNTY and CYRUS R. VANCE, JR., in his official capacity as DISTRICT ATTORNEY OF NEW YORK COUNTY

Defendants.

BRIEF OF CHARISE PFEFFER, ALAN A. PFEFFER, AS *AMICI CURIAE* IN SUPPORT OF THE PLAINTIFFS-APPELLANTS

Dated: February 21, 2017

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QUESTION PRESENTED

Whether the liberty clause of Article I, § 6 of the New York Constitution protects the relationship between a dying patient and her/his doctor permitting the consenting doctor to provide the consenting patient with aid in dying.

INTEREST OF THE *AMICI*

Charise Pfeffer has Huntington's Disease, a non-curable terminal hereditary disease. She watched her mother's slow progression to death caused by Huntington's Disease and knows her future. She has expressed numerous times not wanting to under go the progression she witnessed. Before she departed for a two year tour of service in the U.S.Peace Corp. she completed a health care directive, and appointed a health care proxy. Over the succeeding years she re-issued the documents making the same choices. Her choices included not to prolong her life, not to have treatments that would do so, such as not having artificial life supports, or having a feeding tube installed. She was diagnosed in 2010 shortly before her thirtieth birthday. Approximately a year after diagnosis she re-affirmed her health care choices. If the law allows her to request aid in dying via a health care prior directive, she will do so. She now resides in a specialized Huntington's Disease section of a nursing home in New York. She has an interest in securing physicians and other health care providers who will fully provide advice, care and treatment, especially concerning end of life matters, without fear of being prosecuted under

New York's assisted suicide laws. She is concerned that fear of prosecution will adversely effect their relationship and prevent the full care, treatment and advice she seeks. She seeks the liberty to direct her physician to administer all medications through a prior health care directive and appointed health care agent when she is no longer able to talk, write and swallow regardless of the predicted proximity to death or mental state.

Alan A. Pfeffer is the volunteer advocacy chair for the Albany Chapter of the Huntington's Disease Society of America. The legal positions expressed are his and not the Society's, although the Society is actively considering adopting them. He is a member of the New York State Department of Health's Advisory Committee for Centers of Excellence for Neurodegenerative Disease. He is a spokesperson for people with Huntington's Disease in a variety of forums. He has an interest in his daughter Charise Pfeffer's welfare and the care she receives and that the treating physicians and other medical providers are able to provide such care and advice without fear of prosecution for assisted suicide. He is the appointed health care agent for Charise Pfeffer and has an interest in being able to direct her physician to administer all medications, care and treatments as her health care proxy when she is no longer able to talk, write and swallow regardless of the predicted proximity to death or mental state without concern that he may be prosecuted for criminal solicitation under Section 100 of the Penal Law.

Not all disabled people fear prejudice and discrimination by having the choice of physician aid in dying. It is estimated that there are 1,954 individuals in New York with active Huntington's Disease and 13,190 people are at risk and have a 50 percent chance of inheriting it from their affected parent.

Huntington's Disease is an autosomal-dominant, progressive neurodegenerative disorder with a distinct phenotype, including chorea and dystonia, incoordination, cognitive decline, and behavioral difficulties. Typically, onset of symptoms is in middle-age, but the disorder can manifest at any time. The mutant protein in Huntington's Disease—huntingtin—results from an expanded CAG repeat leading to a polyglutamine strand of variable length. There is currently no cure or treatment which can halt, slow or reverse the progression of the disease. In late stage Huntington's Disease, individuals require assistance in all activities of daily living. Although they are often nonverbal and bedridden in the end stages, people with Huntington's Disease seem to retain some comprehension. Chorea may be severe, but more often it is replaced by rigidity, dystonia, and bradykinesia. Psychiatric symptoms may occur at any point in the course of the disease, but are harder to recognize and treat late in the disease because of communication difficulties. See Walker, F. *Huntington's Disease*, The Lancet vol. 369 218 (Jan. 20, 2007) Exhibit No.1.

Huntington's Disease is so severe that it was included as one of only ten illnesses and diseases to warrant medical marihuana in the original New York medical marihuana law, Pub. Health L.§3360(7)(a)(i), The Compassionate Care Act, ch.90 L. 2014. Everyone with Huntington's Disease is a potential consumer of physician aid in dying and deserves to have this choice in ending her/his life.

Huntington's Disease is always fatal, never goes into remission, and unlike cancer there are no survivors.

PRELIMINARY STATEMENT

The Appellate Division affirmed the order granting defendant's motion to dismiss the complaint brought by terminally ill patients and physicians who sought to provide aid-in-dying. Citing *Washington v Glucksberg* 521 US 702 (1997), the court held that the application of Penal Law §§ 120.30 and 125.15, which prohibit the promoting of a suicide attempt and define manslaughter in the second degree to include the intentional aid to commit suicide, to prosecute physicians who provide aid-in-dying to their terminally ill patients, does not violate the equal protection or due process clauses of the New York State Constitution (Art. 1, §§ 6, 11) because the practice was not an issue where a legitimate consensus had formed.

However, the Supreme Court in *Washington v Glucksberg* acknowledged that the opinion should not forestall further public discussion and that

> "[t]hroughout the nation, Americans are engaged in earnest and profound debate about the morality, legality and practicality of physician-assisted suicide. Our holding permits this debate to continue, as it should in a democratic society (521 US at 705).

In the twenty years since *Washington v Glucksberg*, that debate has continued and the landscape has changed. Several states, Canada and several European nations have enacted aid-in-dying laws and the facts underlying the decision no longer hold true. Physicians who honor the choice of a competent terminally ill for a dignified and peaceful death by providing the means by which the patient can self-administer medication, are performing a compassionate act and prosecution does not further a compelling state interest. Furthermore, a patient's liberty interest in having a choice in his or her medical aid to end an unbearable life no more stops at termination of medical care, as offered by the Appellate Division, than a liberty interest in marriage stops at civil union. To let nature take its course, as opined by the Appellate Division, is contrary to humanity's altering nature in many ways including the alteration of genes.

A fully developed record is required to properly determine the scope of a liberty interest of a person with a fatal illness and her/his doctors. This liberty interest, to control one's life under the New York State Constitution and to have aid in doing so is complex and is more than a simple yes or no. A liberty interest exists under the New York Constitution because New York has always valued, freedom of choice, freedom from loss of dignity, avoidance of needless harm and suffering.

The liberty interest must be patient centered and illness progression determinative. The further the disease progresses, the greater the patient's interest and the lower the State's interest. The liberty interest must be at least as extensive as the liberty interests of people in a persistent vegetative state who are not facing imminent death.

This Court should consider this nation's policy of providing government services and benefits notwithstanding a person's disability. This requires a reasonable accommodation for people with a fatal illness who are unable to make a contemporary request by speaking, writing, or who may be unable to self-administer medication and whose competency cannot be determined. A reasonable accommodation is accomplished through the use of a prior health care directive and designated agent, as permitted for all other health care matters. In the absence of such accommodation, the *Amicus* Charise Pfeffer will be unable to avail herself of her Constitutional rights.

A patient centered, case by case, approach permits the State to have an interest during some stages of the patent's fatal illness. The State interest varies with the patient's medical status, values and beliefs and not subjective criteria such as the projected date of death. *Amici* caution against enshrining six months before death as the point in time when eligibility for physician aid in dying commences. This approach recognizes the diversity of fatal illnesses and their unique

progressions from on-set to death. Only by acknowledging the variation of State interests can the law best protect individual rights.

For example, when a person with Huntington's Disease, who seeks to end her/his life shortly after diagnosis because future death is certain in a cruel and undignified, and painful way, but currently shows limited active symptoms s/he would be protected by State prohibitions on assisting. As a full record would demonstrate, people with Huntington's Disease have a higher rate of suicide ideation and attempts than the general population. See Walker, *Supra*. State protection while the patient is in this stage may be appropriate.

As the disease progresses the physician-patient relationship plays a greater role. During this next stage of illness, the State may require that certain precautions be taken by physicians so that aid in dying is properly and timely administered. One example is to require the physician to have a speciality in palliative medicine and to advise patients of alternative end of life care.

In the later stages when the progression of the disease is such that the patient views life as unbearable and not worth living and death remains a certainty, the patient's liberty interest prevails. Since this is a disease and patient centered approach, artificial and arbitrary guidelines such as "terminal within six months", ability to self-administer, and the limitations of contemporary oral and written

requests are not determinative. So called "safe guards" are actually terms of limitation precluding the people who need the aid the most, long term suffers of progressive illnesses for which there is no cure, no treatment and no miracles around the corner.

So when a person with Huntington's Disease requires a gastric feeding tube to maintain life and refuses it, there should be no question raised about whether the patient is "terminally ill" in light of the potential life extension afforded by the refused medical intervention. That patient should then have an effective choice of whether to suffer for some undermined time period or seek a fast painless demise. A contemporaneous or prior choice made through a lawful directive and not countered by any contemporaneous physical act of attempting to eat or other communication countering the prior directive must be honored. The State in the Family Health Care Decisions Act , N.Y. Pub. Health L. §2994-c *et. seq*. has set forth protocols for similar situations.

ARGUMENT

I. THE DECISION MUST BE REVERSED AND A FULL RECORD DEVELOPED

A. The Appellate Division Gave Undue Weight To The Decision In *Washington v Glucksberg.*

Obergefell v. Hodges 576 U.S. ___ , 135 S.Ct. 2584 (2015) calls into question the validity of the result reached in *Washington v Glucksberg*

521 U.S. 702, 710-11 (1997). Like *Obergefell*, this appeal involves the relationship between two consenting people, a patient and her/his physician.

The bedrock of the Court's decision in *Washington* was the longstanding expression of the commitment to the protection of all human life by almost every State as evidenced by the absence of any permissive assisted suicide laws in almost every State and almost every western democracy. *Washington v. Glucksberg*. Society's values have evolved since 1997. *Obergefell v. Hodges* 576 U.S. ___ , 135 S.Ct. 2584 (2015) lays to rest the presumption that because a liberty did not exist in the past, it shall never exist.

> History and tradition guide and discipline this inquiry but do not set its outer boundaries. See *Lawrence*, supra, at 572. (Citing *Lawrence v. Texas,* 539 U.S. 558,) *Obergefell v. Hodges*, 135 S.Ct. 2584, 2598 (_U.S._ 2015)That method respects our history and learns from it without allowing the past alone to rule the present.
>
> But while *Lawrence* confirmed a dimension of freedom that allows individuals to engage in intimate association without criminal liability, it does not follow that freedom stops there. Outlaw to outcast may be a step forward, but it does not achieve the full promise of liberty. *Obergefell* at 2600 (_U.S._ 2015)

B. **A Full Record Demonstrates That The Underlying Facts In *Washington* Simply Are No Longer True.**

Permitting the development of a full record shows that six States and the District of Columbia have approved physician aid in dying. This Court should take

Judicial notice of these changes. CPLR Section 4511 (a), *Crawford v. Merrill, Lynch, Pierce, Fenner & Smith*,35 NY2d 291, 299, (1974). These changes undermine the factual assumptions made by the majority opinion in *Washington v Glucksberg.* A liberty interest exists under the New York Constitution because New York has always valued, freedom of choice, freedom from loss of dignity, avoidance of needless harm and suffering.

That there are now seven jurisdictions in the United States is a substantial demonstration supporting the recognition by New York of the right to aid in dying as a liberty interest. Those jurisdictions are here listed:

Oregon- The Death With Dignity Act, 127.800 originally enacted as Ballot measure 16 in 1994. http://public.health.oregon.gov/ProviderPartnerResources/EvaluationResearch/DeathwithDignityAct/Documents/statute.pdf.

Washington- The Washington Death with Dignity Initiative 1000 passed November 4, 2008 codified at RCW chapter 70.245 http://app.leg.wa.gov/rcw/default.aspx?cite=70.245

Vermont-18 V.S.A. Chapter 113 http://www.leg.state.vt.us/docs/2014/Acts/ACT039.pdf

Montana- *Baxter v. Montana*, 224 P.3d 1211 (Mont. 2009)

California End of Life Options Act. Stats. 2015, 2nd Ex. Sess., Ch. 1, Sec. 1. Effective June 9, 2016.

Colorado- Proposition 106 End of Life Options Act, passed November 8, 2016 http://www.sos.state.co.us/pubs/elections/Initiatives/titleBoard/filings/2015-2016/145Final.pdf

District of Columbia approved by Council of the District of Columbia, B21-0038 - Death with Dignity Act of 2015 http://lims.dccouncil.us/Legislation/B21-0038

These six states and the District of Columbia comprise almost 16% of the population of the United States. (51,234,311 of a total population of 323,127513). https://www.census.gov

In 2016 New York had identical Bills pending in the Legislature, Senate 7579 and A10059. Predecessor Bills are set forth in the record. (R. 62-67, 83-89) The Assembly Bill advanced out of the Assembly Health Care committee to the Codes Committee. http://nyassembly.gov/leg/?default_fld=&leg_video=&bn=A10059&term=2015&Summary=Y&Actions=Y.

Canada and Four Western European counties also allow physician aid in dying. The laws and practices are not identical but demonstrate how the underlying facts in *Washington* are no longer accurate.[1]

Canada, Statutes of Canada 2016, Chapter 3Bill C-14 (Royal Assent) June 17, 2016. Must be at least 18 years old, have a serious and incurable illness, disease, or disability, be in an advanced state of irreversible decline, and death must be reasonably foreseeable.

Switzerland, since 1942, Article 115 of the Swiss Federal Criminal Code (StGB) decriminalizes assisted suicide by anyone not acting out of selfish motives. No six month standard-medically diagnosed hopeless or incurable illnesses, unbearable pain or unendurable disabilities, are the eligibility criteria.

Netherlands- Termination of Life On Request and Assisted Suicide Act of 2002 authorizes physician aid in dying by physicians in the form of prescribing or injecting medicine to voluntarily requesting patients. Patient's suffering is unbearable and no reasonable alternative exists to alleviate it, physician acts with due care and attention.

Belgium, Act on Euthanasia of May 28th, 2002. Intentional termination of life by physician at patient's request when suffering is unbearable and cannot be

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1 For a comprehensive analysis and comparison of the various European countries and several States, see Lopes. G. Dying with Dignity-A Legal Approach to Assisted Death, (2015)

alleviated otherwise, request must be voluntary and considered, allows the use of a proxy and an advance directive within five years.

Luxembourg, The Euthanasia and Assisted Suicide Law of March 2009. Allows doctors to prescribe or administer medication to terminally ill adults on request.

C. The Record In *Carter v Canada* (Attorney General) Was Extensive.

The trial court in *Carter v. Canada* (Attorney General) 2015 SCC 5 (2015) benefited from some 36 binders of affidavits, transcripts and documents. There were 116 affidavits, some hundreds of pages in length and attached as exhibits many secondary sources. 18 witnesses were cross-examined on their affidavits, including 11 witnesses who were cross-examined on their affidavits before the Court. 2012 BCSC 886 (par.114, 2012). Included in the record:

> "some witnesses described the progression of degenerative illnesses like motor neuron diseases or Huntington's disease, while others described the agony of treatment and the fear of a gruesome death from advanced-stage cancer. Yet running through the evidence of all the witnesses is a constant theme — that they suffer from the knowledge that they lack the ability to bring a peaceful end to their lives at a time and in a manner of their own choosing". *Carter v. Canada* (Attorney General) 2015 SCC 5 (par 14, 2015) (R. 187)

Canada's Supreme Court also benefited from twenty six intervenors. (R. 164-165).

D. A Full Record Would Show The Concerns Of Patients And Their Families

A liberal construction of a complaint on a pre-answer motion to dismiss is required. *Chanko v. Am. Broad. Cos.*, 2016 NY Slip Op 02478, 3 (N.Y. 2016). The courts below failed to recognize, discuss or provide any indication that they considered the wishes of fatally ill patients, and their families, in upholding a distinction between terminating medical care resulting in death and death accomplished with physician assistance. From the patient's and family's perspective it is a distinction without a difference. Withholding medical care is done so as not to prolong the dying process. For people who make the choice not to prolong the dying process, implied is a choice to hasten it. Terminating medical care through the removal of a ventilator is as much an affirmative act as is intravenous insertion of a lethal medicine. For the patient it is medical treatment for unbearable suffering without relief and with no possibility of a cure and a satisfactory outcome. Assistance is necessary for the patient to exercise her/his individual right to choose how to live and die.

II. A. A LIBERTY-PRIVACY-CHOICE INTEREST UNDER THE NEW YORK CONSTITUTION FOR AID IN DYING EXISTS

This Court has found rights protected under Article I, § 6 New York Constitution that are not found under the U.S. Constitution. See *People v. LaValle*, 3 N.Y.3d 88. (2004)

> We note that we have on many occasions interpreted our own Constitution to provide greater protections when circumstances

> warrant and have developed an independent body of state law in the area of search and seizure (see e.g. *People v Scott*, 79 NY2d 474; People v Harris, 77 NY2d 434; *People v Dunn,* 77 NY2d 19; *People v Torres,* 74 NY2d 224, 228). We have adopted separate standards "when doing so best promotes `predictability and precision in judicial review of search and seizure cases and the protection of the individual rights of our citizens'" (*People v P.J. Video*, 68 NY2d 296, 304 [citations omitted]). *People v. Weaver*, 12 N.Y.3d 433, 445 (2009)
>
> In short, independent state constitutional law is no longer considered novel or unusual. It is now routinely accepted and applied as a matter of course. Hancock, Jr., Stewart F., *New York State Constitutional Law —Today Unquestionably Accepted and Applied as a Vital and Essential Part of New York Jurisprudence,* Albany L. Rev. Vol. 77.4, 1331

See also, Eddy, G. *The Development of Independent New York Constitutional Jurisprudence in Chief Judge Kaye's Judicial Opinions: An Empirical Study,*71 Albany L. Rev. 1137 (2009). State Courts have been encouraged to do so. Brennan, Jr.William J, *State Constitutions and the Protection of Individual Rights,* 90 Harv. L. Rev. 489, 491 (1977).

The "right to choose to die" by withholding or withdrawing life-sustaining treatment already exists in New York and has been codified in the Public Health Law Article 29 C sections 2980 *et seq.* New York extends this right of choice to disabled people who were never capable of giving informed consent[2]. It did so

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[2] This law was justified on the grounds that people with mental retardation deserve "health care rights essential to the humane and dignified treatment to which every other citizen is entitled". See The Bill memo accompanying A8466D which became ch.500 of laws of 2002. http://nyassembly.gov/leg/?default_fld=%0D%0A&leg_video=&bn=A8466-D&term=2001&Summary=Y&Actions=Y&Memo=Y&Text=Y

because New York recognizes that all people are entitled to humane and dignified treatment and care. New York Surrogate's Court Procedure Act § 1750-b. Health care decisions for mentally retarded persons. The right of a State to extend that choice to assistance in exercising that right do so was implicitly upheld in *Gonzales v. Oregon*, 546 U.S. 243 (2006).

> The right to privacy, in constitutional terms, involves freedom of choice, the broad, general right to make decisions concerning oneself and to conduct oneself in accordance with those decisions free of governmental restraint or interference (see, *People v Onofre,* 51 N.Y. 2d 476, 485; 2 Rotunda-Nowak-Young, Constitutional Law, Substance and Procedure § 18.26 et seq.). This "right to be let alone" has been called the "most comprehensive of rights and the right most valued by civilized men" (*Olmstead v United States*, 277 U.S. 438, 478 [Brandeis, J., dissenting]). *Matter of Doe v. Coughlin*, 71 N.Y.2d 48, 52 (N.Y. 1987) *cert. denied.* 488 U.S. 879

Amici assert that a right of choice without a means of implementation is no right. The right to a prior health care directive and a designated health care agent to implement the “right to choose to die” by withholding or withdrawing life-sustaining treatment is firm in New York law. Public Health Law §2980 *et. seq. and §2994 et. seq*. for the appointment of surrogates in the absence of a patient’s prior health care directive. The right to a choice exercised through a prior directive must be extended to physician aid in dying for all fatally ill people regardless of estimated proximity to death and capacity.

The privacy and choice rights of a person facing certain death with unbearable pain and suffering must be at least as extensive as a person in a persistent vegetative state who is not facing imminent death.

The use of a prior directive and proxy provides a reasonable accommodation for people who cannot make a contemporary request for physician aid in dying because their illness or disease prevents them from talking, writing, or whose capacity cannot be determined. When the patient is unable to self-administer due to the disease or illness, physician administered is a required reasonable accommodation. The option of physician administered must be made available in order to prevent the "complications" reported by Oregon, including nineteen regurgitations and one regaining consciousness. (R. 326)[3]

The number of people in Oregon who took the medicine, did not retain it, regained consciousness and later died of the underlying illness may be under reported. Aid in dying is a private process usually occurring at home. There is no mandate that the prescribing physician be present to report complications.

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3 The record contains the Oregon Department of Human Services. Tenth Annual Report on the Oregon Death with Dignity Act. March 2008. (R. 331). The Court should also see the Oregon report for year 2010 issued in 2013 reporting that of the 61 patients who ingested medication, 2 did not die after ingestion, and later died of the illness. Judicial notice should be taken of the official governmental report, http://public.health.oregon.gov/ProviderPartnerResources/EvaluationResearch/DeathwithDignityAct/Documents/year13.pdf and set forth as Exhibit No. 2

Physician administered is a reasonable accommodation for those people who are unable to self-administer.[4] The right to choose must be consistent with the protections afforded under the Americans With Disabilities Act, as amended. 42 U.S.C 12101.[5]

> Further, the statute itself does not literally require a showing of "discrimination." A plaintiff can prevail either by showing "discrimination" or by showing "deni[al of] the benefits" of public services. 42 U.S.C. § 12132.
>
> Therefore, we hold that a claim of discrimination based on a failure reasonably to accommodate is distinct from a claim of discrimination based on disparate impact. Quite simply, the demonstration that a disability makes it difficult for a plaintiff to access benefits that are available to both those with and without disabilities is sufficient to sustain a claim for a reasonable accommodation. *Henrietta D. v. Bloomberg*, 331 F.3d 261, 276-77 (2d Cir. 2003)

B. Privacy-Choice -Liberty and State Interests Will Vary

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[4] "In 1991, David Schuman, the Oregon deputy attorney general, was asked by State Senator Neil Bryant whether disabled individuals who could not self-administer would have to be helped to die under the Death with Dignity law. Schulman replied that in the spirt of the state constitution and in accordance with the equal treatment provisions of the Americans with Disabilities Act, Oregon would probably be required to make "reasonable accommodations (to) enable the disabled to avail themselves of the (Death with Dignity) Act's provisions." citing Smith, Wesley J. 2004 "Assisted Suicide in Oregon" Piercing the Myth of Compassion". See, Lopes. G. Dying with Dignity-A Legal Approach to Assisted Death, p. 136, footnote 51 (2015)

[5] Congress enacted the ADA Amendments Act to restore the understanding that the definition of ``disability'' shall be broadly construed and applied without extensive analysis. Congress intended that the primary object of attention in cases brought under the ADA should be whether covered entities have complied with their statutory obligations not to discriminate based on disability. 81 FR 53203 (August 11, 2016)

Recognizing various stages of State interest based on the patient's medical condition, values and beliefs will protect patient's full rights.

> "We think that the State's interest contra weakens and the individual's right to privacy grows as the degree of bodily invasion increases and the prognosis dims. Ultimately there comes a point at which the individual's rights overcome the State interest." *In Re Quinlan*, 70 N.J. 10, 41 (N.J. 1976).
>
> The concern for the preservation of the life of the patient normally involves an interest in the prolongation of life. Thus, the State's interest in preserving life is very high when "human life [can] be saved where the affliction is curable." (Internal Citation omitted). That interest wanes when the underlying affliction is incurable and would soon cause death regardless of any medical treatment. (Citations omitted). The calculus shifts when the issue is not whether, but when, for how long, and at what cost to the individual that life may be briefly extended. *Brophy v. New England Sinai Hospital, Inc,* 398 Mass. 417, 433 (Mass. 1986)[6]

The State interests are the greatest in the early stages of the disease when the patient is diagnosed as having a fatal illness but shows no or limited symptoms. Here the law seeks to protect patients against a premature death. For people with Huntington's Disease the first year after diagnosis is generally a time of many suicides and suicide ideation. See Walker *Supra*. Lack of self-control over her/his destiny is involved. Keeping the patient away from guns and other means of harm are of particular concern.

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[6] In both the *Quinlan* and *Brophy* cases the patients were not terminally ill and not in danger of imminent death. Rather, they were in a persistent vegetative state with no chance of a cognitive recovery. Brophy's attending physician, and the other medical personal, refused to carry out the request to remove the feeding tube because it was their belief that it would constitute a harmful act which would willfully and deliberately produce death. *Brophy v. New England Sinai Hospital, Inc*, 398 Mass. 417, 429 (Mass. 1986).

As the disease progresses, the State's interest diminishes but is not eliminated.[7] Limited regulation such as only permitting self-administration, or designating a specific physician specialization, maybe needed but the patient - physician relationship plays a greater role in decision-making. The practice of the profession of medicine is defined as "diagnosing, treating, operating or prescribing for any human disease, pain, injury, deformity or physical condition". Education Law §6521. The patient's dignity and self-worth may have deteriorated significantly and the pain increased as the ability to self-care has diminished. The patient may still able to eat and swallow but requires a nursing home. The patient may have expressed a desire for aid in dying but the physician may feel that since death is not imminent, absent an intervening cause, the patient is better served by allowing time for an adjustment in the nursing home. After the patient or caregiver has expressed an interest in aid in dying, the State interest would include services such as informing the patient and the family of other end of life services such as hospice.

This approach honors and respects the patient-physician relationship cherished by our society and reflected in the confidentially privilege. CPLR §4504. It is so important that it survives the death of the patient. *See, People v Wilkin*s

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[7] There are standard tools for the evaluation of the progression such as the Total Functional Capacity Rating Score (Also known as the Shoulson and Fahn Staging Scale), See Physician's Guide to the Management of Huntington's Disease, 3rd Ed.P. 8, http://hdsa.org/shop/publications/

(1985) 65 NY2d 172, 176, 490 NYS2d 759; *see also, Prink v Rockefeller Center* (1978) 48 NY2d 309, 422 NYS2d 911.

> The policy objectives of the statute are to: (1) maximize unfettered communication between patients and medical professionals, so that people will not be deterred by possible public disclosure "from seeking medical help and securing adequate diagnosis and treatment;" (2) encourage physicians to candidly record confidential information in medical records, so they are not torn between the legal duty to testify and the professional obligation to honor patient confidences; and (3) protect the reasonable privacy expectations of patients that their sensitive personal information will not be disclosed (Dillenbeck, 73 NY2d at 285 *Chanko v. Am. Broad. Cos*., 2016 NY Slip Op 02478, 3 (N.Y. 2016)

When the patient has progressed significantly her/his rights prevail.[8] The guidelines set forth in Public Health law are instructive. PHL §2994-d. Surrogates make decisions in accordance with "patient's wishes, including the patient's religious beliefs", or if not known

> "the patient's best interests. An assessment of the patient's best interests shall include: consideration of the dignity and uniqueness of every person; the possibility and extent of preserving the patient's life; the preservation, improvement or restoration of the patient's health or functioning; the relief of the patient's suffering; and any medical condition and such other concerns and values as a reasonable

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[8] The pain should be evaluated using the concept of 'total pain,' which argues that suffering is irreducible to physical pain and must be understood in its multiple dimensions: physical, psychological, social, and spiritual. In order to relieve suffering, care for the dying must therefore be similarly holistic. See Hadi,K. *Suffering and Medicalization At The End Of Life: The Case of Physician- Assisted Dying*, Social Science & Medicine 170,188 (2016). http://dx.doi.org/10.1016/j.socscimed.2016.10.010 Citing Clark, D., 1999. *'Total pain', disciplinary power and the body* in the works of Cicely Saunders, 1958-1967. Soc. Sci. Med. 49, 727e736.

person in the patient's circumstances would wish to consider". PHL §2994-d (4)(ii)

Public Health L. §2994-d (4)(b) requires individual based patient-centered approach and not a uniform approach of terminally ill within six months, mentally competent, contemporary oral and written requests. Even when a decision to withhold or withdraw life-sustaining treatment is made the criteria is individualized.

> (ii) The provision of treatment would involve such pain, suffering or other burden that it would reasonably be deemed inhumane or extraordinarily burdensome under the circumstances and the patient has an irreversible or incurable condition, as determined by an attending physician with the independent concurrence of another physician to a reasonable degree of medical certainty and in accord with accepted medical standards. Pub. Health §2994-d (5)(ii)

Late stage Huntington's Disease evidences pain through rigidity, and dystonia. It may not be possible to determine a patient's capacity due to the inability to speak. A patient should not be tortured to prolong the dying process when there is either a contemporaneous expression communicated in any way or expressed by a prior health care directive.

The situation is exemplified where a patient requires a feeding tube in order to obtain nutrition and live. The Complaint set forth an example:

> "Steve wishes not to have to choose between continuing the painful, lingering decline to death, and the relatively quicker route of starving or dehydrating himself to death. Those options, in his considered judgment, deprive him of the integrity and dignity he has left. (R. 29)

Plaintiff's allege and we agree "If a feeding tube is removed, the death will usually be slow and protracted through dehydration and starvation". (R. 36). (A similar situation exists when the feeding tube is needed but not inserted). A true dilemma. Insert the tube and live for some time in an unwanted condition and not meet the criteria of six months, or face a slow starvation[9]. *Amici* seek the choice of a third alternative, physician aid in dying.

At this stage the patient's liberty interest in controlling the course of her/his medical care is paramount and free from physician control or the control of the State. The patient's contemporary, or prior, request for aid in dying and not prolonging the dying process must be honored. When the patient refuses a medically needed feeding tube due to the inability to eat orally, and does not attempt eating or otherwise express a desire to endure, the physician must follow the patient's choice.[10]

Amici caution against enshrining six months as the point of eligibility for physician aid in dying. There is no medical evidence to support the belief that it is at that time when a fatally ill person begins unbearable suffering and also because each fatal disease presents a unique progression. Finally, six months as the initial

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[9] This demonstrates the need for physician administered medicine since the patient who requires a feeding tube is unable to self-administer via swallowing.

[10] Since the feeding tube in most cases will extend life, the physician's question whether the patient is within six months of death is moot.

eligibility time period, copied from the hospice law, is a completely arbitrary standard when applied to aid in dying because it was made part of the hospice program as a federal cost containment provision.[11]

For a patient at this stage, there is no compelling State interest, no "welfare, health or prosperity of the state" causing the individual to sacrifice her/his particular interest or desires that is necessary component that society as a whole shall be benefited. *People v. Lochner*, 177 N.Y. 145, 153 (N.Y. 1904). Nor may the interests of other vulnerable disabled, but not fatally ill, people's need for protection be asserted as a State interest to the determent of the autonomy of the individual patient. Nor may the State assert a particular interest of an organized religion over another religion or individual's autonomy. *Everson v. Board of Education*, 330 U.S. 1, 15 (1947).

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11 The law establishing the Hospice program defines this as: "An individual is considered to be "terminally ill" if the individual has a medical prognosis that the individual's life expectancy is 6 months or less". Enacted as part of the Tax Equity and Fiscal Responsibility Act of 1982, a law designed to contain Medicare and Medicaid cost. There is no legislative history explaining how six months was chosen. See Senate Conference Report, S. No. 97-530. Evidence points to Congress's concern with the cost of the new program, See *Medicare Hospice Benefit-Limitations on Clinical Judgment That a Hospice Enrollee is Terminally Ill Must Be withdrawn,* http:// www.painlaw.org/access-to-hospice/#3, footnote 3. Congress established a maximum cap formula where the denominator was the average cost of care of a cancer patient during the last six months of life. See 97-530 page 37. There is no compelling reason to maintain this definition for a different program in light of the evolving social change that says there are situations when continuing to live is no longer worth the pain and suffering. The six month provision was carried over from the hospice program by the proponents of the Oregon law simply because it was there and without any basis.

At this stage State's interests change from preventing assisted suicide to protecting the privacy, autonomy and liberty interests of the dying patient. This is done through making resources available, training physicians, adequate supplies of medicine, and safeguards preventing "complications". The State's interest is in protecting the patient's family from trauma such as delays in the process and unnecessary intrusions into the family's privacy.

The treating physician's exclusion from criminal prosecution arises out of the patient's rights. The privacy, choice, and liberty rights to do what the individual believes is in her/his best interests and wants to do with her/his body and life.

> "`[A]lso fundamental is the right to be free, except in very limited circumstances, from unwanted governmental intrusions into one's privacy.
>
> "`"The makers of our Constitution undertook to secure conditions favorable to the pursuit of happiness. They recognized the significance of man's spiritual nature, of his feelings and of his intellect. They knew that only a part of the pain, pleasure and satisfactions of life are to be found in material things. They sought to protect Americans in their beliefs, their thoughts, their emotions and their sensations. They conferred, as against the Government, the right to be let alone — the most comprehensive of rights and the right most valued by civilized man." *Olmstead v. United States,* 277 U.S. 438, 478 (1928) (Brandeis, J., dissenting).'" *People v. Onofre*, 51 N.Y.2d 476, 487-88 (N.Y. 1980)

There is no evidence to support the "slippery slope" argument nor the fear that vulnerable populations are at risk. Data from Netherlands and Oregon through 2005 shows the contrary. Battin*, Legal Physician−Assisted Dying in*

Oregon and the Netherlands: Evidence Concerning The Impact On Patients in "Vulnerable" Groups, Journal of Medical Ethics, 2007 Oct; 33(10): 591–597 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2652799/.

> Rates of assisted dying in Oregon and in the Netherlands showed no evidence of heightened risk for the elderly, women, the uninsured (inapplicable in the Netherlands, where all are insured), people with low educational status, the poor, the physically disabled or chronically ill, minors, people with psychiatric illnesses including depression, or racial or ethnic minorities, compared with background populations. The only group with a heightened risk was people with AIDS. While extralegal cases were not the focus of this study, none have been uncovered in Oregon; among extralegal cases in the Netherlands, there was no evidence of higher rates in vulnerable groups. Battin, *Supra*

Amici notes that the 1994 N.Y. State Task Force on Life & the Law is outdated, and lacks validation due to its exclusion of a representative from any neurodegenerative disease. https://www.health.ny.gov/regulations/task_force/reports_publications/when_death_is_sought/taskforc.htm .It focused on depression, HIV and cancer. Although heavily relied on by the court below, it was not subject to cross-examination.

> The patient centered approach is not a novel idea.

> We would go further. Oregon insists that the lethal dose is self-administered, to avoid voluntary euthanasia. To the patient the moral distinction between taking a pill and asking for an injection is slight. But the practical consequence of this stricture is to prevent those who are incapacitated from being granted help to die. Not surprisingly, some of the fiercest campaigners for doctor-assisted dying suffer from

ailments such as motor neurone (sic) disease, which causes progressive paralysis. They want to know that when they are incapacitated, they will be granted help to die, if that is their wish. Allowing doctors to administer the drugs would ensure this.

Oregon's law covers only conditions that are terminal. Again, that is too rigid. The criterion for assisting dying should be a patient's assessment of his suffering, not the nature of his illness. Some activists for the rights of the disabled regard the idea that death could be better than a chronic condition as tantamount to declaring disabled people to be of lesser worth. We regard it as an expression of their autonomy. So do many disabled people. Stephen Hawking has described keeping someone alive against his wishes as the "ultimate indignity". See *The Right To Die,* the Economist June 27, 2015. http://www.economist.com/news/leaders/21656182-doctors-should-be-allowed-help-suffering-and-terminally-ill-die-when-they-choose

Conclusion

***Amici* agree with the Plaintiff that this Court should reverse the Appellate Division's order affirming dismissal of Plaintiffs' Complaint.**

Dated: February 21, 2017 Glenmont, New York

Respectfully submitted,

By:_____

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CERTIFICATION

I certify pursuant to 500.13(c)(1) that the total word count for all printed text in the body of the brief, exclusive the table of contents, the table of authorities and exhibits is 6960 words typed in Times New Roman font with 14 pt size.

Dated: February 21, 2017
Glenmont, New York Respectfully submitted,

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Exhibit No. 1

Seminar

Huntington's disease

Francis O Walker

Lancet 2007; 369: 218–28

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Huntington's disease is an autosomal-dominant, progressive neurodegenerative disorder with a distinct phenotype, including chorea and dystonia, incoordination, cognitive decline, and behavioural difficulties. Typically, onset of symptoms is in middle-age after affected individuals have had children, but the disorder can manifest at any time between infancy and senescence. The mutant protein in Huntington's disease—huntingtin—results from an expanded CAG repeat leading to a polyglutamine strand of variable length at the N-terminus. Evidence suggests that this tail confers a toxic gain of function. The precise pathophysiological mechanisms of Huntington's disease are poorly understood, but research in transgenic animal models of the disorder is providing insight into causative factors and potential treatments.

The hereditary nature of chorea was noted in the 19th century by several doctors,[1–4] but George Huntington's vivid description led to the eponymous designation of the disorder as Huntington's disease.[5] Over the next few decades, the worldwide distribution of the disorder and its juvenile form were recorded. The discovery of the causal *HD* gene (table 1) has stimulated research, and work is now focusing on molecular mechanisms of disease.

See Online for webmovie

Year	Event	Publications (n)*
1374	Epidemic dancing mania described	..
1500	Paracelsus suggests CNS origin for chorea	..
1686	Thomas Sydenham describes post-infectious chorea	..
1832	John Elliotson identifies inherited form of chorea[1]	..
1872	George Huntington characterises Huntington's disease[5]	..
1953	DNA structure elucidated	5
1955	Huntington's disease described in Lake Maracaibo region of Venezuela	13
1967	World Federation of Neurology meeting on Huntington's disease	38
1976	First animal model (kainic acid) of Huntington's disease described[6]	100
1983	Gene marker for Huntington's disease discovered	138
1993	HD gene identified;[7] Huntington study group formed for clinical trials	172
1996	Transgenic mouse developed[8]	242
2000	Drugs screened for effectiveness in transgenic animal models	344

*Approximate number of publications on Huntington's disease cited for that year in the Current List of Medical Literature (before 1966) and in PubMed (1967 onwards).

Table 1: **History of Huntington's disease**

Search strategy and selection criteria

I searched Pub Med from 1965-2005 for the term "Huntington's Disease" cross referenced with the terms "apoptosis", "axonal transport", "mitochondria", "animal model", "proteosome", "transcription", "juvenile", "suicide", "neurotransmitters", "age of onset", "identical twins", "neurodegeneration", and "imaging". I translated all non-English language publications that resulted from this search strategy. I mainly selected articles from the past five years, but did not exclude commonly referenced and highly regarded older publications. I also searched the reference lists of articles identified by this search strategy and selected those that I judged relevant. Several review articles and book chapters were included because they provide comprehensive overviews beyond the scope of this Seminar. The reference list was further modified during the peer-review process based on comments from the reviewers.

Clinical findings in Huntington's disease

Individuals with Huntington's disease can become symptomatic at any time between the ages of 1 and 80 years; before then, they are are healthy and have no detectable clinical abnormalities.[9] This healthy period merges imperceptibly with a prediagnostic phase, when patients show subtle changes of personality, cognition, and motor control. Both the healthy and prediagnostic stages are sometimes called presymptomatic, but in fact the prediagnostic phase is associated with findings, even though patients can be unaware of them.[10] Diagnosis takes place when findings become sufficiently developed and specific.[11] In the prediagnostic phase, individuals might become irritable or disinhibited and unreliable at work; multitasking becomes difficult and forgetfulness and anxiety mount. Family members note restlessness or fidgeting, sometimes keeping their partners awake at night.[4] Eventually, this stage merges with the diagnostic phase (see webmovie), during which time affected individuals show distinct chorea, incoordination, motor impersistence, and slowed saccadic eye movements.[12,13]

Cognitive dysfunction in Huntington's disease, often spares long-term memory but impairs executive functions, such as organising, planning, checking, or adapting alternatives, and delays the acquisition of new motor skills.[4,14] These features worsen over time; speech deteriorates faster than comprehension. Unlike cognition, psychiatric and behavioural symptoms arise with some frequency but do not show stepwise progression with disease severity. Depression is typical and suicide is estimated to be about five to ten times that of the general population (about 5–10%).[14–17] Manic and psychotic symptoms can develop.[4]

Suicidal ideation is a frequent finding in patients with Huntington's disease. In a cross-sectional study, about 9% of asymptomatic at-risk individuals contemplated suicide at least occasionally,[11] perhaps a result of being raised by an affected parent and awareness of the disease. In the prediagnostic phase, the proportion rose to 22%, but in patients who had been recently diagnosed, suicidal ideation was lower. The frequency increased again in later stages of the illness.[11] The correlation of suicidal ideation with suicide has not been studied in people with Huntington's disease, but suicide attempts are not

uncommon. In one study, researchers estimated that more than 25% of patients attempt suicide at some point in their illness.[18] Individuals without children might be at amplified risk,[19,20] and for these people access to suicidal means (ie, drugs or weapons) should be restricted. The presence of affective symptoms, specific suicidal plans, or actions that increase isolation (eg, divorce, giving away pets) warrants similar precautions.[20]

Although useful for diagnosis, chorea (figure 1) is a poor marker of disease severity.[21,22] Patients with early-onset Huntington's disease might not develop chorea, or it might arise only transiently during their illness. Most individuals have chorea that initially progresses but then, with later onset of dystonia and rigidity, it becomes less prominent.[21,22]

Another finding in Huntington's disease that contributes to patients' overactivity is motor impersistence—the inability to maintain a voluntary muscle contraction at a constant level (figure 2).[23] This difficulty leads to changes in position and sometimes compensatory repositioning. Incapacity to apply steady pressure during handshake is characteristic of Huntington's disease and is called milkmaid's grip. Motor impersistence is independent of chorea and is linearly progressive, making it a possible surrogate marker of disease severity.[7]

Fine motor skills, such as finger-tapping rhythm and rate, are useful for establishing an early diagnosis of Huntington's disease: gross motor coordination skills, including gait and postural maintenance, deteriorate later in the disorder's course. Such changes, unlike chorea, directly impair function, a finding that is, in part, indicated by the modern preference for the terminology Huntington's disease rather than Huntington's chorea.

As motor and cognitive deficits become severe, patients eventually die, usually from complications of falls, inanition, dysphagia, or aspiration. Typical latency from diagnosis to death is 20 years.[4]

Huntington's disease in juveniles (onset before age 20 years and as early as 2 years) and some adults can present with rigidity without signs of chorea.[2,24,25] Such individuals can be misdiagnosed with Parkinson's disease, catatonia, or schizophrenia. Slowed saccadic eye movements are usually prominent in these patients—jerking of the head to look to the side is characteristic. Seizures are fairly typical in young patients and cerebellar dysfunction can arise.[24,25] A decline in motor milestones or school performance is sometimes an early finding in children with Huntington's disease.

Differential diagnosis

Diagnosis of Huntington's disease is straightforward in patients with typical symptoms and a family history. However, dentatorubropallidoluysian atrophy,[26] Huntington's disease-like 2 (frequent in black Americans and South Africans),[27] and a few other familial disorders[28,29] are phenotypically indistinguishable from the disorder. Furthermore, about 8% of patients do not have a known affected family member.[30,31] Neuroacanthocytosis can also mimic Huntington's disease,[32] but areflexia, raised creatine kinase, and the presence of acanthocytes are distinctive. Huntington's disease should not be confused with tardive dyskinesia, chorea gravidarum, hyperthyroid chorea, vascular hemichorea, the sometimes unilateral post-infectious (Sydenham's) chorea, and chorea associated with antibodies against phospholipids. By comparison with Huntington's disease, these disorders have a different time course, are not familial, and do not have motor impersistence, impaired saccades, and cognitive decline as characteristics. In young people, Huntington's disease can be confused with hepatolenticular degeneration and subacute sclerosing panencephalitis.

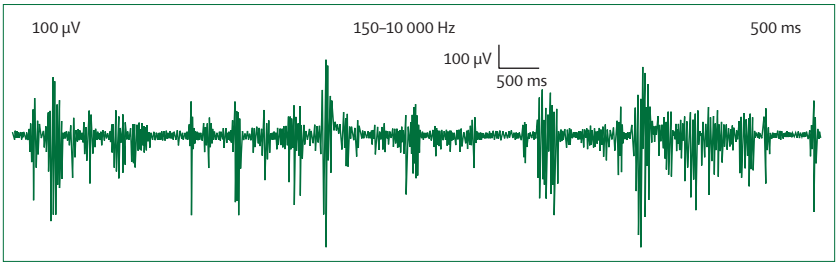


Figure 1: **EMG recording of chorea in patient with stage I Huntington's disease**
Recording is made with standard belly tendon using surface disc electrodes placed over the first dorsal interosseus muscle. Note the irregular pattern of discharges, with variable amplitude, duration, and rise times of every EMG burst. Healthy individuals at rest show no EMG activity.

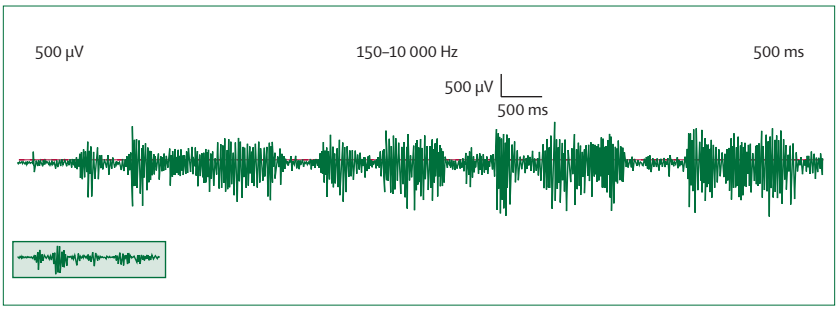


Figure 2: **EMG recording of motor impersistence**
The patient is instructed to maximally abduct the second digit against resistance and to maintain it. Note that motor activity fades repeatedly. The parenthetical inclusion is a copy of the first 400 ms of resting chorea shown in figure 1, adjusted for the different amplitude settings, for comparison. Note that choreiform bursts intermittently exceed the EMG activity from maximum volitional effort. Healthy individuals show consistent EMG amplitude during this task.

Neuropathology

Neuropathological changes in Huntington's disease are strikingly selective, with prominent cell loss and atrophy in the caudate and putamen.[33–35] Striatal medium spiny neurons are the most vulnerable. Those that contain enkephalin and that project to the external globus pallidum are more involved than neurons that contain substance P and project to the internal globus pallidum.[33,34] Interneurons are generally spared. These findings accord with the hypothesis that chorea dominates early in the course of Huntington's disease because of preferential involvement of the indirect

pathway of basal ganglia-thalamocortical circuitry.[11] Other brain areas greatly affected in people with Huntington's disease include the substantia nigra, cortical layers 3, 5, and 6, the CA1 region of the hippocampus,[36] the angular gyrus in the parietal lobe,[37,38] Purkinje cells of the cerebellum,[39] lateral tuberal nuclei of the hypothalamus,[40,41] and the centromedial-parafascicular complex of the thalamus.[42]

In early symptomatic stages of Huntington's disease, the brain could be free of neurodegeneration.[43–45] However, evidence of neuronal dysfunction is abundant, even in asymptomatic individuals. Cortical neurons show decreased staining of nerve fibres, neurofilaments, tubulin, and microtubule-associated protein 2 and diminished complexin 2 concentrations.[46,47] These elements are associated with synaptic function, cytoskeletal integrity, and axonal transport and suggest an important role for cortical dysfunction in the pathogenesis of the disorder.

One of the pathological characteristics of Huntington's disease is the appearance of nuclear and cytoplasmic inclusions that contain mutant huntingtin and polyglutamine.[48] Although indicative of pathological polyglutamine processing, and apparent in affected individuals long before symptom onset,[43] mounting evidence suggests that these inclusions are not predictors of cellular dysfunction or disease activity, which instead seem to be mediated by intermediate stages of polyglutamine aggregates.[49] In some transgenic mouse models of Huntington's disease, inclusions arise only after symptoms begin.[50] Cells that have inclusions seem to survive longer than those without,[51] and little correlation is seen between the various cellular and animal models of the disorder and human Huntington's disease, in terms of the appearance of inclusions in histopathological specimens and the onset of dysfunction or neurological symptoms.[43,50–54] A compound that enhances aggregate formation might actually lessen neuronal pathological findings.[55]

Imaging

Routine MRI and CT in moderate-to-severe Huntington's disease show a loss of striatal volume and increased size of the frontal horns of the lateral ventricles,[56] but scans are usually unhelpful for diagnosis of early disorder. Data from PET and functional MRI studies have shown that changes take place in affected brains before symptom onset,[57–59] and some MRI techniques can precisely measure cortex and striatum.[60,61] In fact, with these techniques, caudate atrophy becomes apparent as early as 11 years before the estimated onset of the disease and putaminal atrophy as early as 9 years.[61] In presymptomatic individuals carrying the *HD* gene who show no evidence of progression by clinical or neuropsychological tests over 2 years, tensor-based magnetic resonance morphometry shows progressive loss of striatal volume.[62]

Clinical genetics

The gene for Huntington's disease (*HD*) is located on the short arm of chromosome four and is associated with an expanded trinucleotide repeat. Normal alleles at this site contain CAG repeats, but when these repeats reach 41 or more the disease is fully penetrant.[34,63,64] Incomplete penetrance happens with 36–40 repeats, and 35 or less are not associated with the disorder. The number of CAG repeats accounts for about 60% of the variation in age of onset, with the remainder represented by modifying genes and environment.[65–71]

Trinucleotide CAG repeats that exceed 28 show instability on replication, which grows with increasing size of the repeat; most instability leads to expansion (73%), but contraction can also take place (23%).[67–69] Instability is also greater in spermatogenesis than oogenesis, in that large expansions of CAG repeats on replication happen almost exclusively in males.[72–74] These findings account for the occurrence of anticipation, in which the age of onset of Huntington's disease becomes earlier in successive generations, and the likelihood of paternal inheritance in children with juvenile onset symptoms. Similarly, new-onset cases of Huntington's disease with a negative family history typically arise because of expansion of an allele in the borderline or normal range (28–35 CAG repeats), most usually on the paternal side.[75]

Somatic instability of CAG repeats also happens in Huntington's disease. Although fairly minor, somatic mosaicism with expansion has been noted in the striatum in human beings and in animal models of the disease,[76–79] and this finding could contribute to selective vulnerability. Mosaicism in lymphocytes might rarely complicate genetic testing.[75]

Identical twins with Huntington's disease typically have an age of onset within several years of each other, but in some cases they show different clinical phenotypes.[76,77] Homozygous cases of the disorder show no substantial differences in age of onset,[78] but the rate of progression can be enhanced.[79]

Genetic testing and diagnosis of Huntington's disease

Despite early surveys that suggested a high amount of interest, fewer than 5% of individuals at risk for Huntington's disease choose to actually pursue predictive genetic testing.[80] Those who undergo testing generally do so to assist in making career and family choices; others elect not to test because of the absence of effective treatment. Predictive testing for the disorder is not without risk. Suicide can follow a positive result,[81,82] and people who are misinformed about the nature of Huntington's disease might seek testing inappropriately. Current protocols are designed to exclude testing for children or those with suicidal ideation, inform patients of the implications of test results for relatives (ie, identical twins), identify sources of subsequent support, and

protext confidentiality.[83–85] Genetic discrimination against individuals with Huntington's disease has been reported but, at least for now, has been rare.[86] Few centres are sympathetic with requests from doctors for help if recommended testing protocols have been ignored.[83–85]

For individuals who undergo pretest counselling, evidence suggests that the overall experience with the process is positive. Although anxiety and stress increase immediately after being given a positive test result, these symptoms return to baseline. Overall, at 2 years, distress is lower and well-being higher irrespective of the outcome of the test.[82] People who receive a negative result can sometimes have stress, known as survivor guilt,[84,87] and subsequent counselling can be of value. Prenatal testing is requested substantially less frequently than predictive presymptomatic testing, a finding attributed to denial, resistance to abortion (an option not needed for preimplantation genetic testing),[88] and concern about fetal risks.[89,90] Parents who opt not to test express hope that treatment will become available for affected offspring.

A positive genetic test is cost effective and provides confirmation for patients who have developed signs and symptoms consistent with Huntington's disease irrespective of family history. Negative test results could lead to diagnosis of a syndrome that resembles Huntingdon's disease. At-risk individuals who have survived to advanced age without developing signs or symptoms sometimes undergo exclusionary testing to allay fears that their children or grandchildren might have inherited the disorder. Experience with genetic testing in Huntington's disease has served as a model for testing protocols for other late-onset disorders and points out the challenges and opportunities of genome technology.[91]

Epidemiology and genetic fitness

Huntington's disease shows a stable prevalence in most populations of white people of about 5–7 affected individuals per 100 000. Exceptions can be seen in areas where the population can be traced back to a few founders, such as Tasmania[92] and the area around Lake Maracaibo[21] in Venezuela. In Japan, prevalence of the disorder is 0·5 per 100 000, about 10% of that recorded elsewhere, and the rate is much lower in most of Asia.[93] African populations show a similarly reduced prevalence,[2,4,94,95] although in areas where much intermarriage with white people takes place the frequency is higher.[2,4,94]

Currently, the higher incidence of Huntington's disease in white populations compared with African or Asian people relates to the higher frequency of huntingtin alleles with 28–35 CAG repeats in white individuals.[34,94] In people with dentatorubropallidoluysian atrophy, which is frequent in Asia, expanded alleles for the causal gene (*ATN1*) are much more typical in Asian populations.[34,93,94]

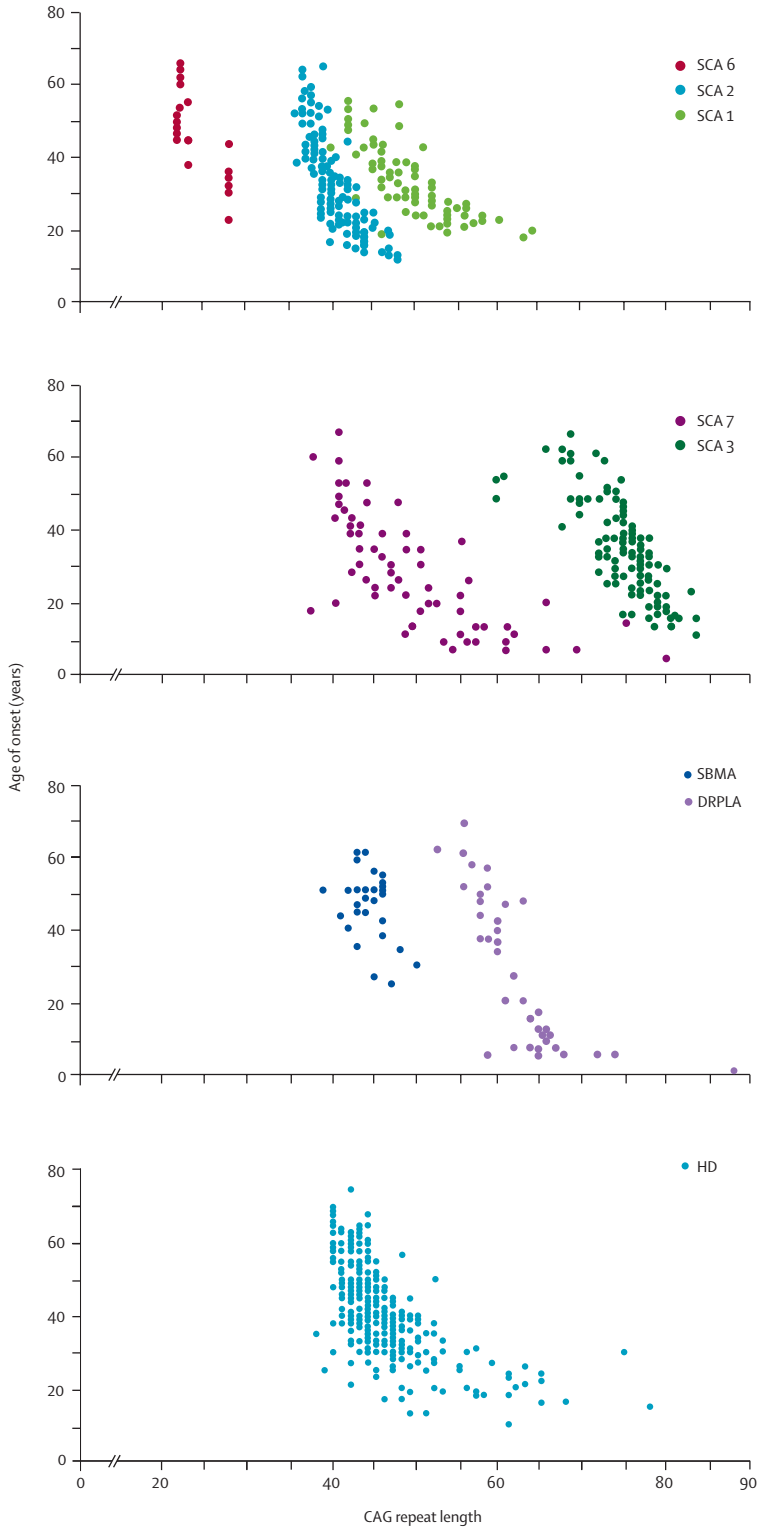
Why do population differences in huntingtin alleles persist? What is the genetic fitness of Huntington's disease? Findings have shown no consistent increase or decrease in the number of children of affected individuals.[4,94] Furthermore, the *HD* gene does not seem to confer any promising health benefits other than a possible lower incidence of cancer,[96] perhaps related to an upregulation of *TP53* in Huntington's disease.[97] No data suggest that expanded huntingtin alleles protect against epidemic infectious disease.

Huntingtin and pathogenesis of Huntington's disease

Huntingtin is expressed in all human and mammalian cells, with the highest concentrations in the brain and testes; moderate amounts are present in the liver, heart, and lungs.[98] Recognisable orthologs of the protein are present in many species, including zebrafish, drosophila, and slime moulds.[99,100] The role of the wild-type protein is, as yet, poorly understood, as is the underlying pathogenesis of Huntington's disease.

One mechanism by which an autosomal-dominant disorder such as Huntington's disease could cause illness is by haploinsufficiency,[101] in which the genetic defect leads to inadequate production of a protein needed for vital cell function. This idea seems unlikely[34,99] because terminal deletion or physical disruption of the *HD* gene in man[101,102] does not cause Huntington's disease. Furthermore, one copy of the *HD* gene does not cause a disease phenotype in mice. Whereas homozygous absence of the *HD* gene is associated with embryonic lethality in animals, people homozygous for the *HD* gene have typical development.[34,79,99]

Findings suggest that the mutant *HD* gene confers a toxic gain of function. A persuasive line of evidence for this idea comes from nine other known human genetic disorders with expanded (and expressed) polyglutamine repeats: spinocerebellar ataxia types 1, 2, 3, 6, 7, 12, and 17; dentatorubropallidoluysian atrophy; and spinobulbar muscular atrophy.[103–113] For none of these disorders is there evidence to suggest an important role for haploinsufficiency. In spinobulbar muscular atrophy, complete deletion of the androgen receptor is not associated with neuromuscular disease.[34,104,105] All nine diseases show neuronal inclusions containing aggregates of polyglutamines and all have a pattern of selective neurodegeneration. One of the most striking features of these disorders is the robust inverse correlation between age of onset and number of polyglutamine repeats (figure 3). Results suggest that the length of the polyglutamine repeat indicates disease severity irrespective of the gene affected, with the longest repeat lengths associated with the most disabling early-onset (juvenile) forms of these disorders. Although difficult to confirm, some data also suggest that the rate of progression might be faster with longer CAG repeats, particularly for individuals with juvenile-onset disease.[114–116]



The most convincing evidence for a gain of function in Huntington's disease is the structural biology of polyglutamine strands. In-vitro evidence suggests that polyglutamines will begin to aggregate, initially by forming dimers, trimers, and oligomers. This process needs a specific concentration of protein and a minimum of 37 consecutive glutamine residues, follows a period of variable abeyance and proceeds faster with higher numbers of glutamine repeats. These findings might account for both delayed onset of disease and the close correlation with polyglutamine length.[117] The rate of aggregation increases with the number of glutamine residues, which accords with evidence showing that length of expansion is associated with early age of onset. Huntington's disease arises only in patients with 36 repeats or more, corresponding to 38 glutamine residues (a normal huntingtin sequence after the poly-CAG tract contains CAA and CAG, which both code for glutamine).[99] Individuals with 36–40 CAG repeats (38–42 residues) show variable penetrance with respect to the Huntington's disease phenotype, with fewer people having symptoms with 36 repeats and only rare cases showing no symptoms at 40 repeats.[34,94] Other CAG-repeat disorders have closely related, but somewhat different, repeat ranges (figure 3) associated with age of onset, but it is noteworthy that only in Huntington's disease is the polyglutamine strand at the N-terminus of the expressed protein. Other characteristics of the expressed proteins in these disorders probably affect aggregation.

The mechanism whereby polyglutamine aggregation leads to selective neuronal dysfunction in Huntington's disease and eventually neurodegeneration has not yet been elucidated, but several key processes have been identified. The first steps seem to involve proteolysis and aggregation, as outlined above. Mutant huntingtin is at higher risk of proteolysis than wild-type protein and its truncation facilitates aggregation.[99,118–121] The polyglutamine strand in the mutant protein occupies only a small proportion of its length,[25] and a shorter protein could reduce steric interference. Evidence suggests that aggregates of truncated huntingtin are toxic and likely to translocate to the nucleus.[49,118–121]

Prolonged mutant huntingtin production and aggregate formation are believed to eventually overcome the ability of cells to degrade them, via either proteasomes or autophagic vacuolisation,[6,34,103] leading to an increased load of unmanageable aggregate proteins. Aggregates also interfere with normal proteins by recruiting some of them into their matrix. Such proteins include those that usually interact with wild-type huntingtin,[34,103,122] suggesting that perhaps truncated and aggregated mutant huntingtin retains active binding sites. Through

Figure 3: **Composite graphs plotting age of onset against number of CAG repeats in eight human polyglutamine disorders**[97,101–107]
Note the tight inverse correlation and the clustering of number of repeats for every genetic disorder. SCA=spinocerebellar ataxia. SBMA=spiobulbar muscular atrophy. DPPLA=dentatorubropallidoluysian atrophy. HD=Huntington's disease.

these and possibly other mechanisms, mutant huntingtin affects several nuclear and cytoplasmic proteins that regulate transcription,[8,34,103] apoptosis,[34,103,123] mitochondrial function,[34,103,124] tumour suppression,[97] vesicular and neurotransmitter release,[46,47,125] and axonal transport.[126] Through the many mechanisms described above, mutant huntingtin might not only have a toxic gain of function but also exert a dominant negative effect, in which it interferes with the typical function of wild-type huntingtin.[52,127,128]

Another step in the pathogenesis of Huntington's disease might entail cell-cell interactions. Mutant huntingtin might cause harm to a neuron, by disrupting the function of nearby neurons or glia that provide important support to that neuron. For example, in a transgenic mouse model of Huntington's disease, interference of mutant huntingtin with the axonal transport and vesicular release of brain-derived neurotrophic factor in corticostriatal neurons seems to contribute to intrinsic dysfunction of striatal neurons.[52,109,110]

Animal models of Huntington's disease

The earliest animal models of Huntington's disease were developed in the 1970s on the basis of selective vulnerability of striatal neurons to excitotoxic aminoacids.[129] These neurons have many glutamate receptors because corticostriatal pathways use this excitatory aminoacid as a primary neurotransmitter. Striatal neurons have also proven to be selectively vulnerable to 3-nitroproprionic acid, a mitochondrial toxin, suggesting that Huntington's disease might affect energy metabolism in neurons.[130]

Transgenic animal models of Huntington's disease were first created in mice[131] and subsequently in *Drosophila* spp and *Caenorhabditis* elegans.[132,133] The fly and mouse models consistently show neuronal polyglutamine inclusions and indicate that pathology is dependent on polyglutamine length, is late onset, progressive, motor, and degenerative, with neuronal dysfunction followed by neuronal death.[133] Similar animal models of other inherited polyglutamine disorders have been developed.[103,132,133]

Although post-mortem human brain tissue from end-stage Huntington's disease patients is available, animal models are invaluable because they provide material for histopathological and biological studies in the earliest stages of disease pathogenesis and for assessment of cell-cell interactions.[52] The transgenic animal models also allow insertion of modifying genes and blinded drug treatment trials.[99,132,133] For example, in a transgenic mouse model in which expression of mutant huntingtin protein with 94 polyglutamines could be switched off, not only was the clinical syndrome reversed but also

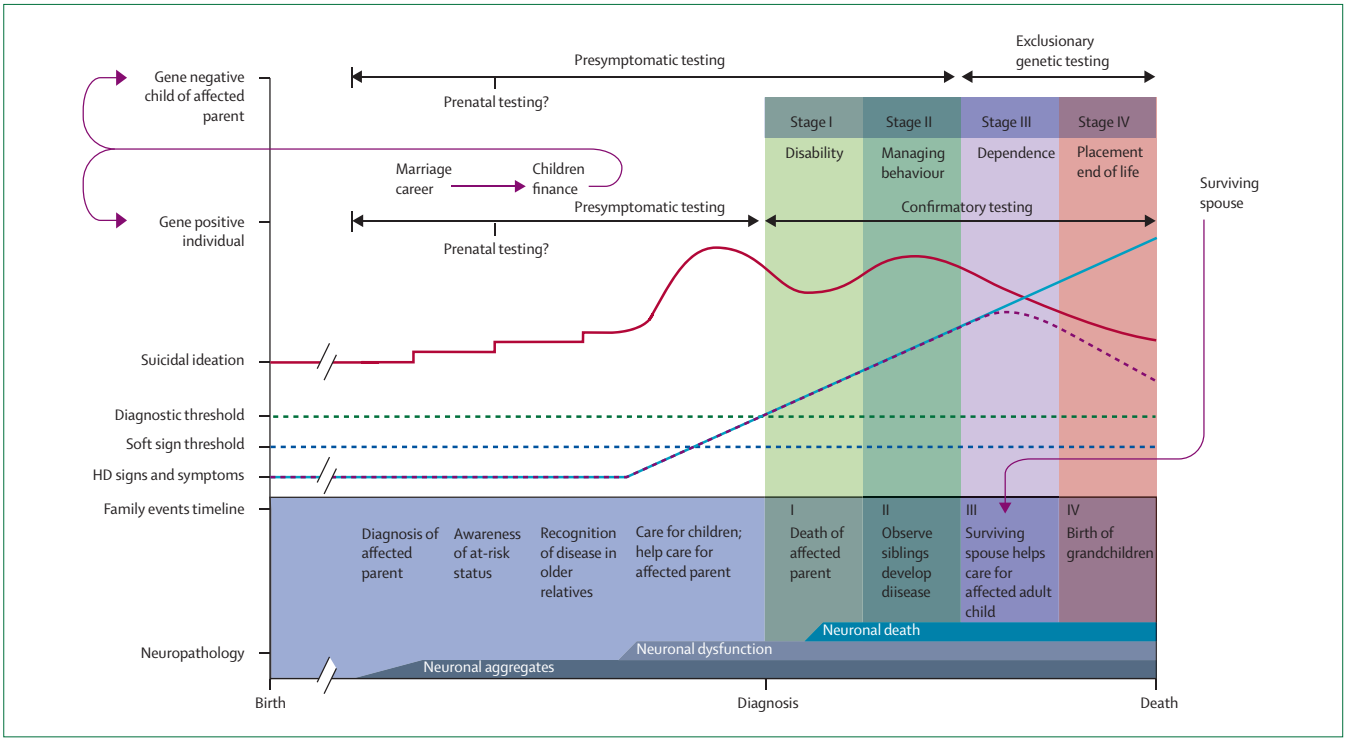


Figure 4: **Life cycle in Huntington's disease**
This figure depicts the sequential evolution of events and ultimately recurrent nature of Huntington's disease from the perspective of a child born to an affected parent. The family events timeline shows events that might occur in different sequences for different individuals; irrespective of timing, such events can have clinically significant implications.

***Panel:* Behavioural difficulties and symptoms in patients with Huntington's disease[10,14]**

Apathy or lack of initiative
Dysphoria
Irritability
Agitation or anxiety
Poor self-care
Poor judgment
Inflexibility

Frequent symptoms (20–50% of patients)
Disinhibition
Depressed mood
Euphoria
Aggression

Infrequent symptoms (5–12%)
Delusions
Compulsions

Rare symptoms (<5%)
Hypersexuality
Hallucinations

Drugs with reported benefit	Interventions with reported benefit	No benefits noted
Lithium	Stem cell transplants	Rofecoxib
Creatine	Environment enrichment	Dichloroacetate
Trehalose	Intrabodies	Aspirin
Paroxetine		Asialoerythropoietin
Clioquinol		S-PBN
Mercaptamine		
Sirolimus		
Remacemide		
Minocycline		
Phenylbutyrate		
Thioetic acid		
Gabapentin-lactam		

Table 2: **Potential treatments for Huntington's disease tested in transgenic animal models**

Drugs with reported symptomatic benefit (chorea only)	Drugs in clinical trials	No protective benefit recorded
Amantadine	Creatine	Baclofen
Remacemide	Riluzole	Vitamin E
Levetiracetam	Ethyl eicasapentaenoic acid	Lamotrigine
Tetrabenazine	Mercaptamine	Remacemide
	Minocycline	
	Phenylbutyrate	
	Coenzyme Q 10	
	OPC-14117 (Otsuka Pharmaceuticals, Tokushima, Japan)	
	Tauroursodeoxychalic acid	

Table 3: **Potential treatments for Huntington's disease tested in human trials**

pathological inclusions were resolved.[134] Work done in transgenic animal models might not always be applicable to human Huntington's disease because of species differences and variations in huntingtin gene length, promoters, and mechanisms of expression.[99,132] Nonetheless, the ability to test drugs in an animal that has a lifespan of days or months provides a useful model for screening compounds that would need years of testing in patients.

Symptomatic treatment of Huntington's disease

Diagnosis of Huntington's disease usually happens when patients seek medical advice with respect to difficulties with work. In such situations, a diagnosis might be partly welcome because it helps to establish disability. People who are doubtful about having Huntington's disease, however, could benefit from a delay in diagnosis until a follow-up visit, when laboratory confirmation is available and they are supported by a family member. The visit at which a diagnosis of Huntington's disease is made is especially important clinically. Family members might recall it in particular detail, so providing accurate information about genetics and sources of support is vital. Making the experience as positive as possible—by dispelling myths and identifying strategies for good family experiences—establishes a professional bond that can be helpful later should difficulties arise.

Like other chronic diseases, managing patients with Huntington's disease requires a proper appreciation of the limitations of medical management. Despite research advances in the past 20 years, medical treatment has made little progress. The survival of affected individuals in the Lake Maracaibo region of Venezuela, where medical technology is largely unavailable, is similar to that of populations with ready access to treatments.[14] Antichoreic drugs such as tetrabenezine[135] or neuroleptics offer patients with severe chorea a respite from their constant involuntary movements. However, declining function might not be an indication for increasing these drugs because they can cause bradykinesia, rigidity, and depression or sedation. Affective disorders in Huntington's disease are amenable to psychiatric treatment, so prompt intervention is advisable.

Counselling can be helpful for patients, their spouses, and individuals at risk for Huntington's disease. Even though only a few patients take advantage of predictive or prenatal testing, frank discussions can help them deal with the complex issues of family, financial, and career planning (figure 4). Support groups are invaluable sources of information and insight that can help patients and families through the recurring difficulties of Huntington's disease.

Behavioural aspects of Huntington's disease can be especially troublesome. In the doctor's office, patients and family members sometimes belabour the cosmetically distracting motor symptoms of the disorder, such as

dystonia or chorea, and might need direct questioning to describe treatable affective disorders or disruptive symptoms such as irritability or compulsions. Poor hygiene, impaired judgment, impulsiveness, and aggression can happen as well (panel).[136,137] Sometimes, acknowledging the difficulties faced by families and caregivers is all that can be done.

Patients with Huntington's disease love to eat, yet weight loss is typical in these individuals.[138] Discussion of food preferences is an enjoyable part of seeing such patients in the clinic. However, as their disease progresses, feeding becomes increasingly difficult, with dysarthria, dysphagia, and difficulty getting food into the mouth. Smaller bites, use of thickening agents, and reminders not to eat quickly may be of benefit.[139]

Experimental treatments

Currently, several drugs for Huntington's disease are in clinical trials to slow the progression of the disease; a few agents have shown promise in work done in animal models.[140,141] The most intriguing research to date has been with coenzyme Q10, which has shown effectiveness in transgenic animal models of Huntington's disease and a possibility of improvement in a human trial.[142] This substance is believed to work by enhancing mitochondrial function in Huntington's disease. A long-term clinical trial of high doses of coenzyme Q10 in patients with Huntington's disease has received federal funding and will begin soon.

However, for completion, standard clinical trials of drugs such as coenzyme Q10 take several years and entail many patients. One way to speed up assessment of promising treatments is with futility studies.[143] This type of study design—by prudent use of historical controls and predetermination of what constitutes a desirable magnitude of effect—can be used as an intermediate step to screen compounds for definitive trials. Such studies are especially useful when risks of long-term side-effects from treatment are possible or when funding and suitable volunteers are in limited supply. This type of study is currently being used to test minocycline, a drug with unique anti-inflammatory and antiapoptotic effects, in Huntington's disease. Tables 2 and 3 list other potential drugs.

The development of surrogate markers of Huntington's disease for clinical trials might also be a promising way to assess new treatments quickly and safely. Use of disease markers to monitor progression of cancer or HIV has accelerated the pace of drug discovery for these disorders. Current interest in Huntington's disease has focused on imaging biomarkers,[61] but the potential for serological markers is also of interest.[144–146] A promising study has shown that Huntington's disease transgenic mice without caspase 6 do not develop symptoms. Therefore, treatment of Huntington's disease in humans by interfering with the catabolism of mutant huntingtin by this enzyme could be possible.[147]

Future work

The best therapeutic option for Huntington's disease could entail starting treatment in the asymptomatic phase of the disorder. Currently, in several observational studies of at-risk individuals, the feasibility of using the onset of the clinical Huntington's disease phenotype or other biomarkers of disease (such as changes on imaging studies) is being investigated as a potential endpoint for future clinical trials.[148] Successes in animal models, identification of possible surrogate markers, progress in symptomatic treatment,[149] and design of efficient study designs all provide tangible reasons for optimism in the Huntington's disease community. With adequate funding for continued research, the discovery of meaningful treatment seems imminent.

Conflict of interest statement

I declare I have no conflict of interest.

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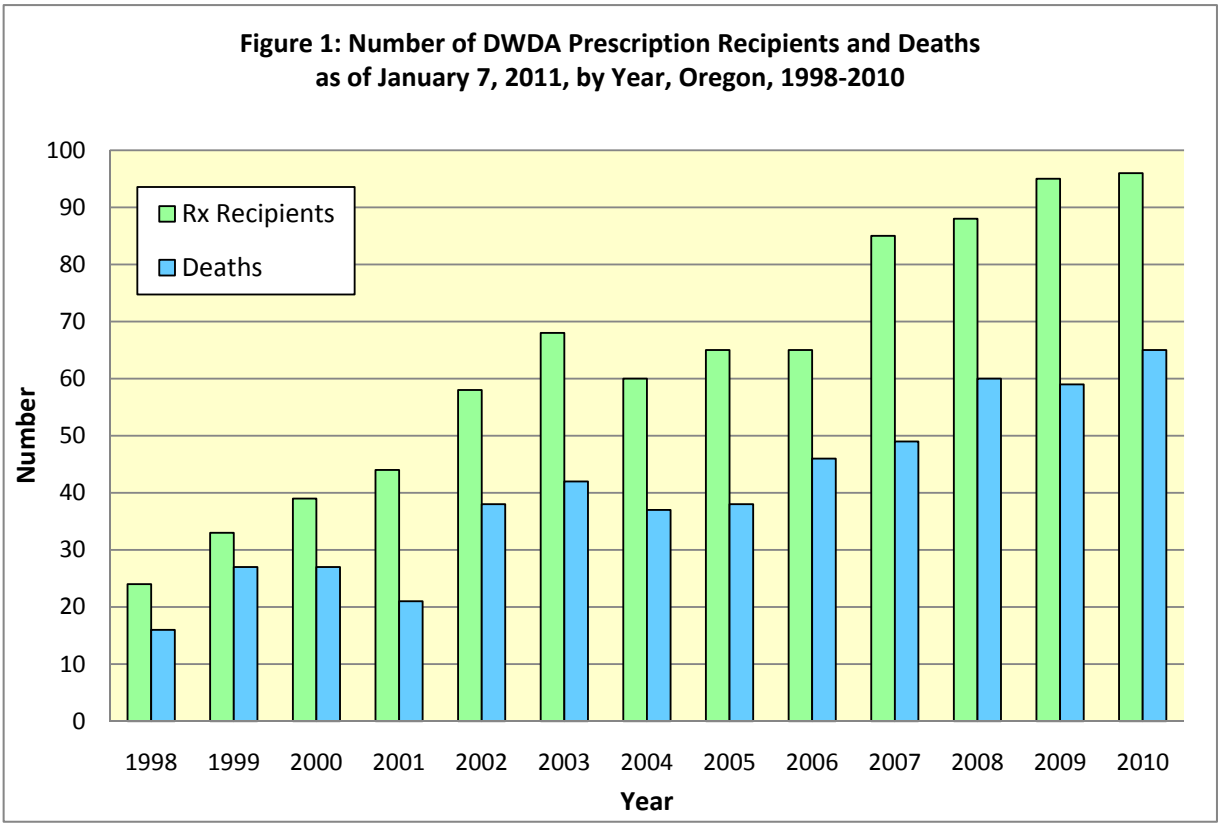
Exhibit No. 2

Oregon's Death with Dignity Act--2010

Oregon's Death with Dignity Act (DWDA), enacted in late 1997, allows terminally-ill adult Oregonians to obtain and use prescriptions from their physicians for self-administered, lethal doses of medications. The Oregon Public Health Division is required by the Act to collect information on compliance and to issue an annual report. The key findings from 2010 are listed below. The numbers of prescriptions written and deaths contained in this report are based on paperwork and death certificates received by the Public Health Division as of January 7, 2011. Because there is sometimes a delay between a death and receipt of the follow-up questionnaire and death certificate, it is possible that additional participants that received the medications in 2010 have died, but the Public Health Division has not yet received the paperwork or the death certificate. For more detail, please view the figures and tables on our web site at http://oregon.gov/DHS/ph/pas/index.shtml.

Figure 1: Number of DWDA Prescription Recipients and Deaths as of January 7, 2011, by Year, Oregon, 1998-2010



- As of January 7, 2011, 96 prescriptions for lethal medications had been written under the provisions of the DWDA during 2010, compared to 95 during 2009 (Figure 1). Of the 96 patients for whom prescriptions were written during 2010, 59 died from ingesting the medications. In addition, six patients with prescriptions written during previous years ingested the medications and died during 2010 for a total of 65 known 2010 DWDA deaths at the time of this report. This corresponds to 20.9 DWDA deaths per 10,000 total deaths.

- Two of the patients who took the medications during 2010 did not die after ingestion, but died later from their underlying illness. Twenty of the patients who received prescriptions in 2010 did not take the medications and died of their underlying illness. Status is pending for 15 patients: two have died but we have not received the follow up questionnaire, and for 13 we have neither the death certificate nor follow up questionnaire (Figure 2).

- One of the two patients who awoke after ingesting the medication regained consciousness within 24 hours after ingestion and died of their underlying illness five days later; the other gained consciousness 3 ½ days after ingestion and died of their underlying illness three months later. Regurgitation was reported in both instances.

- Fifty-nine (59) physicians wrote the 96 prescriptions written in 2010 (range 1-11).

- Since the law was passed in 1997, 525 patients have died from ingesting medications prescribed under the Death with Dignity Act.

- Of the 65 patients who died under DWDA in 2010, most (70.8%) were over age 65 years; the median age was 72 years. As in previous years, most were white (100%), well-educated (42.2% had a least a baccalaureate degree), and had cancer (78.5%).

- Most (96.9%) patients died at home; and most (92.6%) were enrolled in hospice care at time of death. Most (96.7%) had some form of health care insurance, although the number of patients who had private insurance (60.0%) was lower in 2010 than in previous years (69.1%), and the number of patients who had only Medicare or Medicaid insurance was higher than in pervious years (36.7% compared to 29.6%).

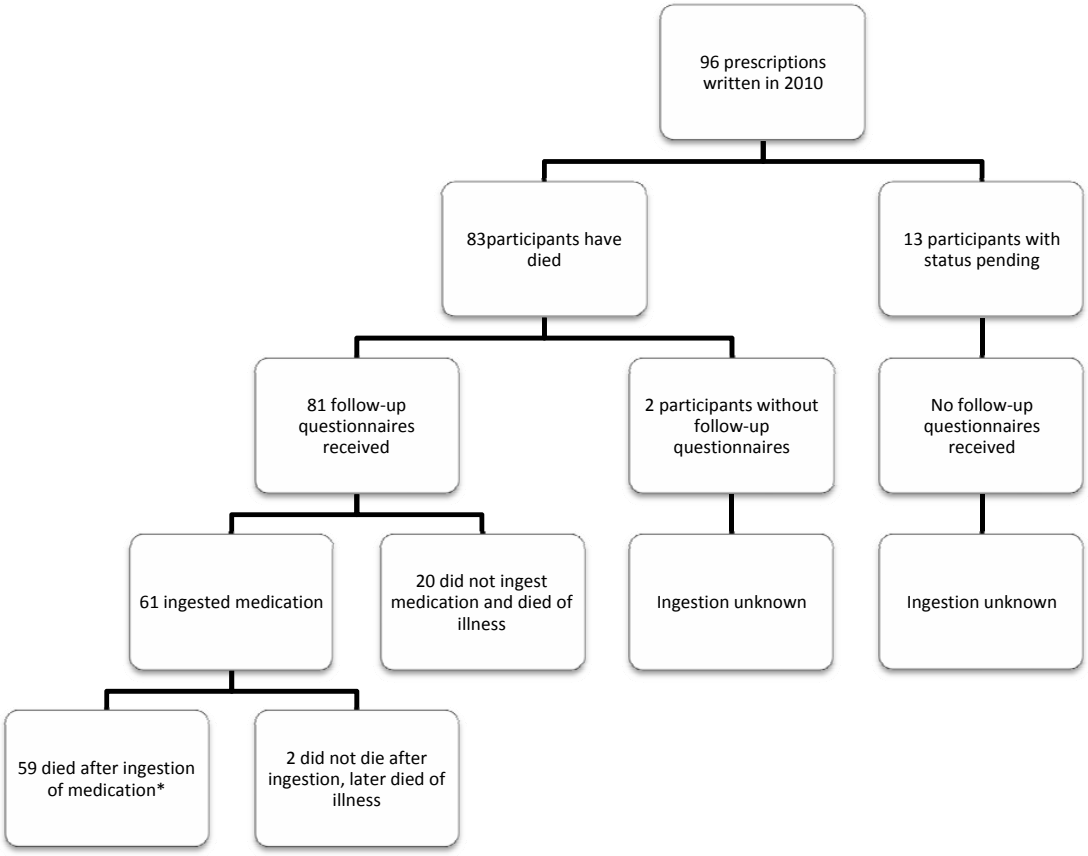
- As in previous years, the most frequently mentioned end-of-life concerns were: loss of autonomy (93.8%), decreasing ability to participate in activities that made life enjoyable (93.8%), and loss of dignity (78.5%).

- In 2010, one of the 65 patients was referred for formal psychiatric or psychological evaluation. Prescribing physicians were present at the time of death for six (9.4%) patients compared to 20.3% in previous years.

- Procedure revision was made mid-year in 2010 to standardize reporting on the follow-up questionnaire. The new procedure accepts information about time of and circumstances surrounding death only when the physician or another health care provider was present at the time of death. Due to this change, data on time from ingestion to death is available for only 32 of the 65 deaths in 2010. Of those 32 patients, time from ingestion until death ranged from 5 minutes to 2.2 days (53 hours).

- During 2010, one referral was made to the Oregon Medical Board for failing to wait 48 hours between the patients written request and writing the prescription.

Figure 2: Outcome of the 96 participants for whom prescriptions were written under the provisions of DWDA in 2010, as of January 7, 2011



* An additional six patients with prescriptions written in previous years died from ingestion of medication in 2010, for a total of 65 known 2010 DWDA deaths at the time of this report.